Exhibit C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION — MDL NO. 2327

THIS DOCUMENT RELATES TO: WAVE 1 TVT CASES

DEFENDANT ETHICON'S EXPERT REPORT OF TIMOTHY A. ULATOWSKI, M.S.

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I. Qualifications

I am a consultant on matters concerning medical device regulations, policies, and procedures administered by the Food and Drug Administration (FDA) and associated industry standards and practices. I am an independent consultant and maintain a registered business in the State of Virginia and the County of Fairfax, Virginia under the name Ulatowski Consulting, LLC.

I was awarded a Bachelor of Science degree in 1974 with a major in Microbiology from the Pennsylvania State University. In 1987 I was awarded a Master of Science degree in Physiology/Emphasis in Biomedical Engineering from the Georgetown University School of Medicine in a collaborative program with Catholic University Department of Engineering. I have additional college credits in computer science from the University of Maryland and Charles County Community College.

I was employed by the FDA from November 1974 until January 2011. During my 36 plus years of employment with FDA I held increasingly responsible positions, first for 7 years in what is now known as the Center for Drug Evaluation and Research (CDER), and the remaining years in the Center for Devices and Radiological Health (CDRH). CDRH is responsible for evaluation and clearance or approval of new medical devices, evaluation of medical device clinical investigations, ensuring compliance with medical device laws and regulations administered by the FDA, postmarket vigilance of marketed devices, and research on emerging device technologies.

From 1974 until 1978 I held the position of Microbiologist in the National Center for Antibiotic Analysis where I conducted laboratory analyses on antibiotics for regulatory certification purposes. From 1978 until 1980 I held the position of Consumer Safety Officer (CSO) in the Office of New Drug Evaluation (ONDE). While in ONDE I was a product manager for the Anti-inflammatory Drugs Group and I also contributed to the Oncology and Radiopharmaceutical Drugs Groups. I was the Executive Secretary for the Arthritis Advisory Committee and managed the flow of work and outputs concerning investigational new drug applications (INDs) and New Drug Applications (NDAs). I also was the division lead on major issues such as the Drug Efficacy Study Implementation (DESI) program and the Radiopharmaceutical Drug Research Committee program. In this capacity I became expert in FDA drug regulations, policies, and procedures.

In 1980 I joined the Office of New Device Evaluation (NDE), Program Management Group, in the Bureau of Medical Devices (BMD) as a CSO. BMD was soon reorganized and joined with the Bureau of Radiological Health to form CDRH. NDE was renamed the Office of Device Evaluation (ODE).

I was assigned to the Investigational Device Staff and was responsible for formulating policies and procedures to implement the newly effective investigational device exemptions regulation, 21 CFR Part 812, and other new human subject protection regulations, 21 CFR Parts 50 and 56. I evaluated investigational device exemption applications (IDEs) including protocols for clinical studies. I also evaluated and quality controlled the IDE review work of all the divisions in ODE.

In 1988 I was promoted to the Director of the IDE Staff. In that capacity I was responsible for managing and directing the IDE staff, for making final decisions on the sufficiency of IDE applications and the review of those submissions by FDA staff, and for IDE regulatory compliance in collaboration with the Office of Compliance, CDRH. In this position I became thoroughly knowledgeable about IDE regulations, policies and procedures, clinical studies and when those studies may be needed to substantiate the safety and effectiveness of devices, as well as associated industry standards and practices.

Later in 1988 I transferred to the position of Branch Chief, General Hospital Devices in ODE. My position classification changed to Supervisory Biomedical Engineer. As Branch Chief I managed and directed the branch staff, and was a primary reviewer of IDE applications, Premarket Notification Submissions (510(k)s), Premarket Approval Applications, new product labeling, medical device reports (MDRs) and other types of regulatory submissions under the purview of my branch. My branch evaluated products classified by FDA under 21 CFR Part 880, General Hospital Devices. The products in this classification regulation include, for example, infusion pumps and ports, administration sets and intravascular catheters. In this position I became thoroughly knowledgeable about premarket submission and medical device reporting regulations, policies and procedures, as well as associated industry standards and practices.

In 1991 I was promoted to the position of Associate Director for General Devices in ODE. The scope of my responsibilities expanded to include the premarket evaluation of surgical devices classified under 21 CFR Part 878 as well as the previously assigned general hospital products. In this capacity I had broader influence on guidance, policy and procedure development spanning the entire ODE. I formulated guidance, policies and took numerous premarket actions on many significant new products such as medical lasers and computerized medical systems.

In 1996 I was promoted to the Director, Division of Dental, Infection Control and General Hospital Devices in ODE. In this position I assumed responsibility for more product areas and all the premarket regulatory activities associated with those product areas. During the course of my tenure as Division Director, I assumed responsibility for even more types of devices such as anesthesiology devices.

During my tenure at FDA I participated as a member on national and international standards committees and the Global Harmonization Task Force (GHTF). I was the co-chair of the committee that created the existing standards program in CDRH. The CDRH standards program evaluates national and international standards to determine if FDA should recognize and utilize them as means to support product development and premarket submissions. The GHTF created internationally harmonized medical device regulatory guidance documents now used around the globe. During this time I also wrote the first FDA guidance documents on infusion pumps and accessories, infusion ports, sterilizers, chemical germicides, and guidance on labeling of devices intended for reuse.

In 2003 I was promoted to Director, Office of Compliance, CDRH. As the office director I supervised a large staff that was responsible for ensuring compliance with the medical device, radiological health, and human subject protection laws and regulations administered by FDA. I

had many duties including, for example: managing inspections of manufacturing facilities and clinical investigation sites; evaluating Quality System(QS), MDR, and recall-related inspection reports; evaluating and directing advisory or enforcement actions; classifying recall actions; creating FDA risk management strategies; evaluating advertising, labeling and promotional literature; directing actions on violations of the medical device reporting regulation; leading the FDA Device Field Committee, which is composed of chief inspectors and senior compliance officers, and; managing responses to violations of import/export and registration laws and rules. In this position I became thoroughly knowledgeable about FDA law and regulations concerning medical devices and associated industry standards and practices.

I transitioned to the position of Senior Advisor for Enforcement in October 2010 in anticipation of my retirement and to allow an orderly succession of leadership. During the last four months of my FDA career I led a team formulating strategies in advance of Congressional user fee reauthorization and I provided expert advice to senior FDA leadership on premarket and compliance programs. The Commissioner awarded me for my work on user fee legislation.

During my employment with FDA I received virtually every type of award FDA can bestow including the Distinguished Career Service Award, Award of Merit, Commendable Service Awards, and numerous other individual and group awards. I maintained my management and regulatory expertise during the course of my career by attending numerous professional meetings, courses and seminars. I was frequently an invited speaker or major participant at regulatory and professional conferences here and abroad such as those held by the Food and Drug Law Institute, Regulatory Affairs Professional Society, and the American Medical Association. I remain current on FDA matters.

I now am an independent consultant working on medical device regulatory issues such as premarket submissions, postmarket surveillance, promotion and advertising, and quality systems. I advise medical device and drug manufacturers on premarket and compliance issues, and provide expert testimony on FDA-related regulatory matters in litigations. I continue to be an invited speaker at professional and industry meetings. At the request of the US government I trained international regulators on medical device premarket and postmarket programs in 2013 and 2014.

A copy of my curriculum vitae is attached as Appendix A.

I am being compensated in this litigation through NDA Partners LLC. The rate they charge for my services to Butler Snow is $500/hr.

II. FDA's Mission, Statutory and Regulatory Provisions Relevant to the Subject Case

FDA is a consumer protection agency that has roots stretching back to the turn of the last century. Its statutory authority is derived from the Federal Food, Drug, and Cosmetic Act (the act) (21 USC 301 et seq.)[1] and other acts that have been amended from time to time. Regulations

[1] References to the act are stated according to United States Code.

implementing the statutory provisions are published in Title 21, Code of Federal Regulations (21 CFR). The medical device amendments to the act were enacted on May 28, 1976.

FDA regulates medical devices. Tension Free Vaginal Tape (TVT) is a medical device. A medical device is defined under 21 USC §321(h) as:

> *"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or (3) intended to affect the structure or function of the body in man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependant upon being metabolized for the achievement of its primary intended purposes."*

FDA regulates the entire life cycle of medical devices. For example, FDA evaluates investigational studies for new products before the studies commence[2], it inspects manufacturing facilities[3], it evaluates marketing applications, and it monitors device safety and effectiveness during the entire course of their use. FDA regulations govern each of these activities and FDA makes available related guidance documents to be used by industry, FDA staff and the public.

A. FDA's Medical Device Program

CDRH is the primary organization within FDA that regulates medical devices. Other FDA Centers also have authority to regulate medical devices using device law and regulations. Combination products are therapeutic or diagnostic products that consist of more than one regulated article, e.g., drug/device, biological/device. Each combination product is regulated by one primary Center.

CDRH has over 1000 employees and is organized into offices. For example, ODE is responsible for review of new products, except for in-vitro diagnostics and radiologic products, the Office of Compliance (OC) is responsible for compliance and enforcement activities and the Office of Surveillance and Biometrics (OSB) is responsible for evaluating postmarket surveillance reports, epidemiology and statistical reviews. Information from each office within CDRH is integrated in computer systems available for all employees to access and use in the course of performing their jobs. For example, a compliance officer in the Office of Compliance can easily access postmarket reports, inspection records, and premarket records for specific companies. CDRH leverages the considerable manpower in the

[2] FDA does not approve "non-significant risk" devices before studies commence. This evaluation and approval is delegated to institutional review boards (21 CFR Part 56).

[3] FDA has authority to inspect all facilities subject to inspection, e.g., all places related to quality system and medical device reporting activities (21 USC §374).

Office of the Associate Commissioner for Regulatory Affairs in order to conduct inspections, and it uses special government employees and third parties for premarket review activities.

CDRH obtains information on medical devices for review and analysis by many means. For example, it receives required submissions according to procedures in regulations, it proactively collects information and evidence during inspections, it uses public sources of information, and increasingly it relies on regulatory bodies in other countries to provide information to it on regulated products. FDA has extensive test facilities and conducts laboratory and engineering analyses on regulated products for compliance, premarket and postmarket surveillance purposes. Manufacturers generate the data and information in premarket submissions.

B. Prohibited Acts, Misbranding and Adulteration and FDA Enforcement of Laws and Regulations It Administers

The F,D &C Act prohibits specific acts or the causing thereof. Two relevant prohibitions to this litigation under are adulteration and misbranding.[4] The act prohibits the following, in part:

> Introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded;
>
> Adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce; and
>
> Receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

1. Adulteration

The act deems a device to be adulterated, in part (paraphrased):[5]

> If it is a device and the methods used in, or the facilities or controls used for, its manufacture, packing, storage, or installation are not in conformity with applicable good manufacturing practices.

2. Misbranding

The act deems a device to be misbranded, in part (paraphrased):[6]

> If its labeling is false or misleading in any particular;
>
> Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological

[4] 21 USC §331.
[5] 21 USC §351(h).
[6] 21 USC §352.

> conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement;
>
> It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in labeling thereof;
>
> If a notice or other information respecting it was not provided as required by such section or section 510(k); or
>
> For which there has been a failure or refusal to give required notification or to furnish required material or information such as section 519, medical device reports.

The act also provides the following regarding misbranding:[7]

> "If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual."

The misbranding provisions of 21 USC §§352(q) and (r) relating to advertising for devices do NOT apply to TVT devices because TVT devices are not restricted devices.[8]

3. Enforcement of the Laws and Regulations Administered by FDA

The FDA Regulatory Procedures Manual (RPM)[9] directs FDA personnel on internal procedures to be used in processing domestic and import regulatory and enforcement matters. While the RPM is intended mainly to provide guidance to FDA inspectors, investigators, and compliance officers, the document is useful to all of FDA and informative to the device industry.

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[7] 21 USC §321(n).

[8] Devices must designated by FDA as "restricted," either by a regulation promulgated under 21 USC §360j(e)), or by a premarket approval application (PMA) approval order pursuant to 21 USC §360e(d)(1)(B)(ii)). Neither applies to TVT devices.

[9] FDA Regulatory Procedures Manual, http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176446.htm.

The RPM describes the actions FDA may take to ensure compliance with the laws and regulations it administers. Those actions include advisory, administrative, judicial and import actions, and recall, emergency and other procedures. The key offices responsible for these medical device actions and procedures include the Office of Compliance/CDRH, the staff of the Associate Commissioner for Regulatory Affairs, and the FDA Chief Counsel's office. Other offices contribute only as needed.

According to the RPM, "When it is consistent with the public protection responsibilities of FDA and depending on the nature of the violation, it is FDA's practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. **Warning and Untitled Letters**, both advisory actions, are issued to achieve voluntary compliance and to establish prior notice. The use of these letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law."

The FDA compliance offices may exercise enforcement discretion when deciding whether to take enforcement action. Also, the RPM notes "there are instances when issuing a Warning Letter is not appropriate, and, as previously stated, a Warning Letter is not a prerequisite to taking enforcement action. Examples of situations where the agency will take enforcement action without necessarily issuing a Warning Letter include:

1. The violation reflects a history of repeated or continual conduct of a similar or substantially similar nature during which time the individual and/or firm has been notified of a similar or substantially similar violation;
2. The violation is intentional or flagrant;
3. The violation presents a reasonable possibility of injury or death;
4. The violations, under Title 18 U.S.C. 1001, are intentional and willful acts that once having occurred cannot be retracted. Also, such a felony violation does not require prior notice. Therefore, Title 18 U.S.C. 1001 violations are not suitable for inclusion in Warning Letters; and,
5. When adequate notice has been given by other means and the violations have not been corrected, or are continuing."

Relevant administrative actions include Section 305 notices (Citations), Section 305 meetings, administrative detention of devices, and civil money penalties (CMPs). **Detention and civil money penalties** are the most common actions taken. FDA may detain devices for a period of up to 30 calendar days if, during an inspection, the FDA has reason to believe the devices are adulterated or misbranded. The intent of administrative detention is to protect the public by preventing distribution or use of violative devices until FDA has had time to consider the appropriate action to take and, where appropriate, to initiate a regulatory action. The action of choice, in most cases, is a seizure. CMPs are monetary penalties that are assessed by FDA for violations of the law and regulations.

Some relevant judicial actions include seizure, injunction and prosecution. For a **seizure**, the United States of America, as plaintiff,

proceeds under the Supplemental Rules for Certain Admiralty and Maritime Claims (Supplemental Rules) by filing a Complaint for Forfeiture and obtaining a warrant for arrest of the device, directing the United States Marshal to seize (take possession or place in constructive custody of the court) the device. An **injunction** is a civil judicial process initiated to stop or prevent violation of the law, such as to halt the flow of violative products in interstate commerce, and to correct the conditions that caused the violation to occur. FDA can refer cases to the Department of Justice for **criminal prosecution.**

As part of import operations the government may **refuse to admit** devices for import and can **detain** devices upon import. Section 801(a) of the Federal Food, Drug, and Cosmetic Act directs the Secretary of the Treasury to issue a Notice of Refusal when it appears from examination of samples, or otherwise, that an imported shipment is in violation. This Section also orders the destruction of any such shipment refused admission, unless it is exported within 90 days of the date of the notice, or within such additional time as may be permitted pursuant to such regulations. FDA may refuse to admit devices based on information, *other than the results of examination of samples* that causes an article to appear to violate the Act.

Two common additional procedures are the **regulatory meeting** and "**It has come to our attention**" letters. A Regulatory Meeting is a meeting requested by FDA management, at its discretion, to inform responsible individuals or firms about how one or more products, practices, processes, or other activities are considered to be in violation of the law. FDA is not required to hold a Regulatory Meeting and, except for a few specifically defined areas, is not required to provide any other form of notice before taking an enforcement action. An "It has come to our attention letter" may be issued by the Office of Compliance where a potential violation has been observed and FDA requests information to assess the activity. It is not an advisory or enforcement letter.

Advisory, enforcement or other compliance actions are generally initiated by the Office of Compliance[10] or the Associate Commissioner for Regulatory Affairs' office based upon potential violations identified by many sources, e.g., inspections, public or industry complaints, FDA surveillance of public information, or internal agency referrals. Only compliance and enforcement staff with the delegated responsibility can initiate, process or issue an enforcement or advisory action.

The Office of Compliance assesses internal agency referrals of a potential violation, e.g., a referral from the Office of Device Evaluation. The Office of Compliance's initial assessment includes, for example, a determination if the referral describes an activity that may be a violation, whether there is adequate documentation of the activity, and an analysis of the risk to the public health.

[10] The Office of In-Vitro Diagnostic Devices and the Office of Surveillance and Biometrics can initiate compliance actions but the actions must be processed and approved through the Director of Compliance.

4. Regulations Concerning Designing and Testing Medical Devices Prior to Marketing

The development and marketing of a medical device has been characterized as a life cycle. The cycle begins with a concept for a new or modified device, proceeds through design phases, the design is transferred to manufacturing and the device is placed on the market. The cycle is complete when the device becomes obsolete or is modified.

The Design Controls provisions of the FDA Quality System regulation, 21 CFR §820, provide the requirements a manufacturer must incorporate into its design and development procedures and processes. Design controls consist of requirements for (1) design and development planning, (2) identifying all appropriate design inputs, (3) defining design outputs, (4) ensuring that design reviews are conducted at periodic intervals, (5) verifying that design outputs meet design inputs requirements, (6) validating that the finished device meets user needs, and (7) transfer of the design to manufacturing. Documentation of design activities is captured in the Design History File. Design changes are a managed process with the need for such actions as review and approval of changes, verifications and revalidation of the design, when needed, before implementing the changes.

FDA recognizes that manufacturers are constantly developing new and improved devices and bringing these devices to the market even while prior versions of the same type of device continue to be legally marketed. The prior devices often remain on the market until the manufacturer decides to discontinue the previously marketed devices for marketing reasons.

There is no requirement to tell FDA in a PMA or 510(k) about next generation devices in the development pipeline. Manufacturers' design and quality data concerning devices being developed are subject to FDA inspection.

Risk management is the systematic application of management policies, procedures, and practices to the tasks of identifying, analyzing, controlling, and monitoring risk.[11] Risk management is intended to be a framework within which experience, insight, and judgment are applied to successfully manage risk. Risk analysis, part of risk management, is required by the quality system regulation. Risk management as a whole process, while not a requirement of the quality system regulation, is addressed in quality system guidance because of its importance on all aspects of the life cycle of a device.

Risk management begins with the initial development of the design input requirements and assessment of risks known or anticipated at the initial stages of product design. In this way, unacceptable risks can be identified and managed earlier in the design process when changes are easier to make and less costly. Failure Modes and Effects Analyses (FMEAs), Risk Management Reports, and Device Design Safety Analyses

[11] See discussion of risk management in FDA Design Control Guidance, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm. The International Standards Organization (ISO) Standard 14971:2007 is commonly utilized to develop the processes and procedures associated with risk management activities.

(DDSAs) are examples of commonly used tools in the design and risk management processes.

Risk management is an iterative process. As new information becomes available about risk the manufacturer should assess this information and take action as appropriate and practicable to mitigate the risk.

Probability estimation and determination of a probability score is a part of risk analysis. ISO 14971:2007 states:[12]

"Seven approaches are commonly employed to estimate probabilities:
-Use of relevant historical data
-Prediction of probabilities using analytical or simulation techniques
-Use of experimental data
-Reliability estimates
-Production data
-Post-production information
-Use of expert judgment"

Severity is also a risk analysis factor. The manufacturer determines how many levels of severity there are for a particular risk assessment and how the levels are defined.[13] Each level has an associated score.

Risk acceptability is typically displayed on a severity versus probability table with acceptable, unacceptable and as low as reasonably possible regions defined by the manufacturer. All risks should be reduced to the lowest level practicable based on technical and economic factors.

Manufacturers often use risk priority numbers (RPN) in their analyses. The RPN is a value determined by multiplying scores of severity by occurrence by detection. Risk reduction actions affect the RPN by lowering the RPN. Manufacturers often have cut-off values for RPNs to define highest priority risks to address.

If a risk is not acceptable, as determined by the manufacturer, after risk reduction measures have been applied then a risk/benefit analysis determines if the benefit outweighs the residual risk. The ISO standard provides that the risk/benefit decision is made by "experienced and knowledgeable individuals."[14] These individuals may be, for example, medical staff.

5. Regulations Concerning Paths to the Market; Premarket Notification Submissions (510(k)s)

a. Paths to the Market

There are two main regulatory paths to the market for medical devices. One path is FDA approval of a premarket approval application and the other is by FDA clearance of a premarket notification submission,

[12] ISO 14971:2007, Section D.3.2.2; Manufacturers sometimes use the probability cut points described in the standard when devising their risk procedures.
[13] ISO 14971:2007, Section D.3.3.
[14] ISO 14971:2007, Section D.6.1.

commonly known as a 510(k) submission. The path most appropriate for a device depends primarily on its FDA regulatory classification. For purposes of this report on the Ethicon TVT devices, I will concentrate on the 510(k) submission pathway to classification and clearance for marketing.

The act establishes three classes of devices, Class I, II, and III.[15] The act provides regulatory controls for each class to provide reasonable assurance of safety and effectiveness for devices within the class. Class I is subject to "General Controls" including, for example, adulteration and misbranding, registration and listing, adverse event reporting, and good manufacturing practice (quality system requirements). In addition to General Controls, Class II devices are subject to "Special Controls" that may include, for example, specific guidance and patient registries. Class III devices are subject to Premarket Approval but also must meet General Controls.

FDA, based on the recommendations of panels of experts, classified all devices on the market on May 28, 1976 into one of the three classes based upon their assessment of safety and effectiveness of those devices. The devices were grouped into generic types. The classification for each type of device is in 21 CFR, Parts 862-892.

For specific devices not on the market on May 28, 1976 the act provides that any device intended for human use which was not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976 is classified in class III unless the device is substantially equivalent to a type of device (a predicate device) classified into class I or II. FDA determines whether the new device is substantially equivalent to a predicate by means of what the act describes as a "report" submitted to FDA preceding introduction of the device into interstate commerce.

The act describes the form and manner of the "report".[16] It provides, in part, that each person who is required to register and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, "report" to FDA (in such form and manner as FDA shall by regulation prescribe) (1) the class in which the device is classified under Section 360c or if such person determines that the device is not classified under such section, a statement of that determination and the basis for such person's determination that the device is or is not so classified, and (2) action taken by such person to comply with requirements under 21 USC §360d (standards) or Section 360e (premarket approval) which are applicable to the device. These original fundamental provisions of a 510(k) "report" have been expanded, defined, and enriched in several amendments to the act after 1976.

The term "substantially equivalent", which I have noted above, is at the core of classification by means of a 510(k) submission. An amendment to the act in 360c(i) incorporated a definition of the term that FDA had previously included in guidance. According to the act, substantial equivalency means that the new device has the same intended use as the predicate device and the same technological characteristics,

[15] 21 U.S.C. §360c.
[16] 21 U.S.C. §360(k).

or if it does not have the same characteristics then information submitted demonstrates that the new device is as safe and effective as the predicate and does not raise different questions of safety and effectiveness than the predicate device. The FDA review criteria for a 510(k) incorporates this statutory provision and expands upon it.

b. Premarket Notification Submissions

The 510(k) regulation, 21 CFR §807.81, describes when a 510(k) is required. In part, a 510(k) is required for a device being marketed for the first time or for a marketed device that is to be significantly changed or modified in design, components, method of manufacture, or intended use.

The regulation under 21 CFR §807.87 also describes information required in a 510(k). The 510(k) must include, in part: labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use; comparisons to other legally marketed devices, and; any other information FDA needs to determine substantial equivalence.[17] FDA's review of 510(k) data and information for implants is rigorous and thorough.

There is FDA guidance pertaining to 510(k)s. Some FDA guidance applies to the submission process in general[18] while product-specific guidance, if available, provides more details on format and content for a 510(k) or PMA, such as standards that should be applied, tests and results and specific labeling recommendations. Good Guidance Practices (GGPs) state "You (for instance a manufacturer) may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations."[19] GGPs also state "Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence."

FDA issued guidance for surgical mesh, which is the generic type of device under which TVTs are included.[20] The guidance recommends that 510(k)s for surgical mesh include, in part: a summary of safety and effectiveness or a statement that such information is available upon request, specification of all material components of the device, manufacturing information, packaging information, product characterization, and labeling. The document states a final consideration that additional information may be required as technological advances continue but it does not specifically identify the need for clinical data.

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[17] "any other information" may include, for example, preclinical or clinical data, or revised labeling.

[18] 510(k) Submission Process, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm.

[19] 21 CFR §10.115.

[20] Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073790.htm.

There are three types of 510(k) submissions including traditional, special and abbreviated. Traditional submissions can be used under any circumstances and include all information typically required for a 510(k). Abbreviated submissions may include less information than a traditional submission because this submission method relies on "declarations of conformity" to FDA-recognized standards used in support of the design and manufacturing of the type of device. These declarations reduce the amount of standards-related data submitted. A special 510(k) may be used when a manufacturer wishes to significantly modify a legally marketed device. The latter two processes are described in FDA guidance.[21]

FDA may determine, by order, a 510(k) submission to be substantially equivalent (SE), SE with limitations,[22] not substantially equivalent (NSE), or provide a letter that additional information is needed to render a decision (AI). FDA considers a device that is found SE by means of a 510(k) to be "cleared." A device is "approved" only by an approval decision rendered by FDA for a premarket approval application.

Prior to the Safe Medical Devices Act of 1990 (SMDA)[23] manufacturers could go to market after 90 days of submission of the 510(k) unless FDA intervened beforehand with either a call to the submitter to "hold" the review clock, or by an Additional Information (AI) or Not Substantially Equivalent (NSE) letter. The current language in the standard AI letters that "You may not market this device until…you have received a letter from FDA allowing you to do so" was included in the form AI letter after SMDA in 1990 because after SMDA an FDA order was needed allowing the marketing of the device. There is only one format for AI letters even though, in my experience, the above stipulations of the letter are not enforced in certain cases.[24] The AI letter is also an administrative letter issued by ODE, i.e., it is not a compliance action.

FDA notes that there are "…many changes in the evolution of a device."[25] A manufacturer determines that a new 510(k) is needed according to regulation when:

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[21] The New 510(k) Paradigm: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm.

[22] Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to 98-1), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082162.htm.

[23] SMDA, The Safe Medical Devices Act of 1990 (P.L. 101-629), which amended the FFD&C Act (21 U.S.C. 201 et seq.), was signed into law on November 28, 1990.

[24] Two cases of enforcement discretion include (1) changes to a device submitted in a 510(k) after a recall. (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080297.htm), and (2) submission of a 510(k) after FDA requests voluntary submission and ODE makes a referral to OC, e.g., a prior change to a marketed device is deemed significant by FDA.

[25] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device.

> "the device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:
> (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
> (ii) A major change or modification in the intended use of the device."[26]

The FDA guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997"[27] was developed to help assist manufacturers in deciding when a change to a device was "significant" or "major." FDA notes in the guidance "To be certain that a decision on when to submit a 510(k) is correct, one would probably need to enumerate all device types and all potential types of changes and then match each combination of device and change with a decision. Given that there are thousands of individual device types and possibly tens or hundreds of enumerable changes, this would be an impossible task. Furthermore, the resultant guidance would fill volumes, would probably be difficult to use, and would be unlikely to keep pace with an ever-changing technology."

While the guidance tries to provide general guidance on making decisions regarding changes to devices it is clear that FDA relies heavily on manufacturer compliance with the Quality System (QS) regulation as the fundamental means of ensuring device safety and effectiveness. The guidance states, "For many types of changes to a device, it may be found that a 510(k) is not necessary, and the Agency may reasonably rely on good manufacturing practices (either as implemented under the 1978 GMP or the Quality Systems regulation) to continue to assure the safety and effectiveness of the changed device. This reliance is enhanced when manufacturers document their decision-making based on their testing results or other design validation criteria." Also, manufacturers "must have a process in place to demonstrate that the manufactured device meets the change in design specifications (or the original specifications, if no change was intended). They must keep records, and these records must be made available to an FDA inspector." The guidance states, "No matter how carefully this guidance is applied, there will still be decisions in a "gray area" <u>that manufacturers will have to make</u> (emphasis added)."[28] Manufacturers are encouraged, <u>but not required (emphasis added)</u>, to contact FDA when the proposed change is not addressed in the guidance flowcharts. In fact, in my experience it was rare that a manufacturer called my division in ODE to request an opinion on a change to a marketed device.

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[26] 21 CFR §807.81(3).
[27] FDA Guidance, Deciding When to Submit a 510(k), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.
[28] Ibid.

It was reported in 2008 that there are more than 20,000 companies worldwide and 80,000 brands and models of devices.[29] So, based on the fact that FDA notes there are numerous changes with devices, there are probably tens of thousands of changes in any given year. However, there were only 3363 510(k)s submitted in 2008, and only 653 were special 510(k)s.[30] Various conclusions could be drawn from these data but it is evident that relatively few changes to marketed devices result in new 510(k) submissions.

FDA proposed a revision to the K97-1 guidance in 2011 based upon its current thinking about changes to devices. Congress rebuked FDA due to the content of the guidance, requiring the following extraordinary actions in the recently enacted Food and Drug Safety and Innovation Act:[31]

> "Not later than 18 months after the date of enactment of this paragraph, the Secretary shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report regarding when a premarket notification under subsection (k) should be submitted for a modification or change to a legally marketed device. The report shall include the Secretary's interpretation of the following terms: 'could significantly affect the safety or effectiveness of the device', 'a significant change or modification in design, material, chemical composition, energy source, or manufacturing process', and 'major change or modification in the intended use of the device. The report also shall discuss possible processes for industry to use to determine whether a new submission under subsection (k) is required and shall analyze how to leverage existing quality system requirements to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of safety and effectiveness of modified devices."
>
> The law also states "The Secretary shall withdraw the Food and Drug Administration draft guidance entitled 'Guidance for Industry and FDA Staff—510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device', dated July 27, 2011, and shall not use this draft guidance as part of, or for the basis of, any premarket review or any compliance or enforcement decisions or actions."

Congress directed FDA to keep in place the K97-1 guidance until Congress concurred with any new FDA guidance on the issue as noted above.

The upshot of these recent mandatory statutory provisions related to modifications to marketed devices and the need to submit a new 510(k) is that Congress is telling FDA (1) there is a need for industry and

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[29] Advamed. The 510(k) Process: The Key to Effective Device Regulation, 8/19/08.
[30] ODE Annual Report 2008. Special 510(k)s are meant for changes to marketed devices.
[31] Significant Amendments to FDCA, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm20027187.htm.

FDA consensus on the definition of terms used in the 510(k) regulation related to modification of devices, suggesting even the K97-1 guidance and processes are unsatisfactory, (2) Congress will not tolerate a stringent or expanded interpretation of when a 510(k) is needed for a change to a device, as was the case in the withdrawn 2011 guidance, and (3) compliance with the QS regulation should be used as a foundation for "reasonable assurance of safety and effectiveness of modified devices."

As noted, by law Congress rejected FDA's "current thinking" on regulation of changes to marketed devices. The future report to Congress on modifications to devices will serve to recalibrate FDA's thinking to Congressional intent. There is the potential Congress may find as too stringent prior FDA decisions to require 510(k)s for some modifications to marketed devices.

In the recent law Congress uses the terms "reasonable assurance of safety and effectiveness" related to regulation of modified 510(k) devices and not "substantial equivalence" thus further blurring the line between premarket approval and premarket notification.

c. How FDA Determines Substantial Equivalence

FDA reviewers in ODE and OIVD primarily use the decision flowchart first described in a 1986 FDA guidance document when determining substantial equivalence and documenting their decision.[32]

The document describes the key decision elements in determining substantial equivalence, as follows:

> *"Thus, as a matter of practice, CDRH generally considers a device to be SE to a predicate device if, in comparison to the predicate device:*
>
> *the new device has the same intended use (as discussed below); and,*
>
> *the new device has the same technological characteristics, (i.e., same materials, design, energy source, etc.); or, it has new technological characteristics that could not affect safety or effectiveness; or*
>
> *it has new technological characteristics that could affect safety or effectiveness, and*
>
> *-- there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and*
>
> *-- there are data to demonstrate that the new technological features have not diminished safety or effectiveness."*

The document describes decision aspects when determining whether the new device has the same intended use as the predicate as follows:

> *"While a new device must have the same intended use as a*

[32] Guidance on the CDRH Premarket Notification Review Program 6/30/86. (K86-3),510(k) Memorandum #K86-3: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm.

predicate device in order to be SE, the Center does not require that a new device be labeled with precise therapeutic or diagnostic statements identical to those that appear on predicate device labeling in order for the new device to have the same intended use. Label statements may vary. Certain elements of a predicate device's labeled indication may not be critical to its intended therapeutic, diagnostic, prosthetic, surgical, etc., use. The Center's scientific expertise enables it to exercise considerable discretion in construing intended uses in the labeling and promotional materials for predicate and new devices. Thus, a new device with the same intended use as a predicate device may have different specific indication statements, and, as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use, the new device may be found SE.

For the purposes of determining whether or not the new device has the same intended use as a predicate device, the Center assesses any difference in label indications in terms of the safety and effectiveness questions they may raise. The Center considers such points as physiological purpose (e.g. removes water from blood, transports blood, cuts tissue), condition or disease to be treated or diagnosed, professional or lay use, parts of the body or types of tissue involved, frequency of use, etc. If a new device is determined to have the same intended use, the Center may then proceed to determine whether or not it is substantially equivalent. (Devices which do not have the same intended use cannot be substantially equivalent.)"

For technological differences the guidance states:

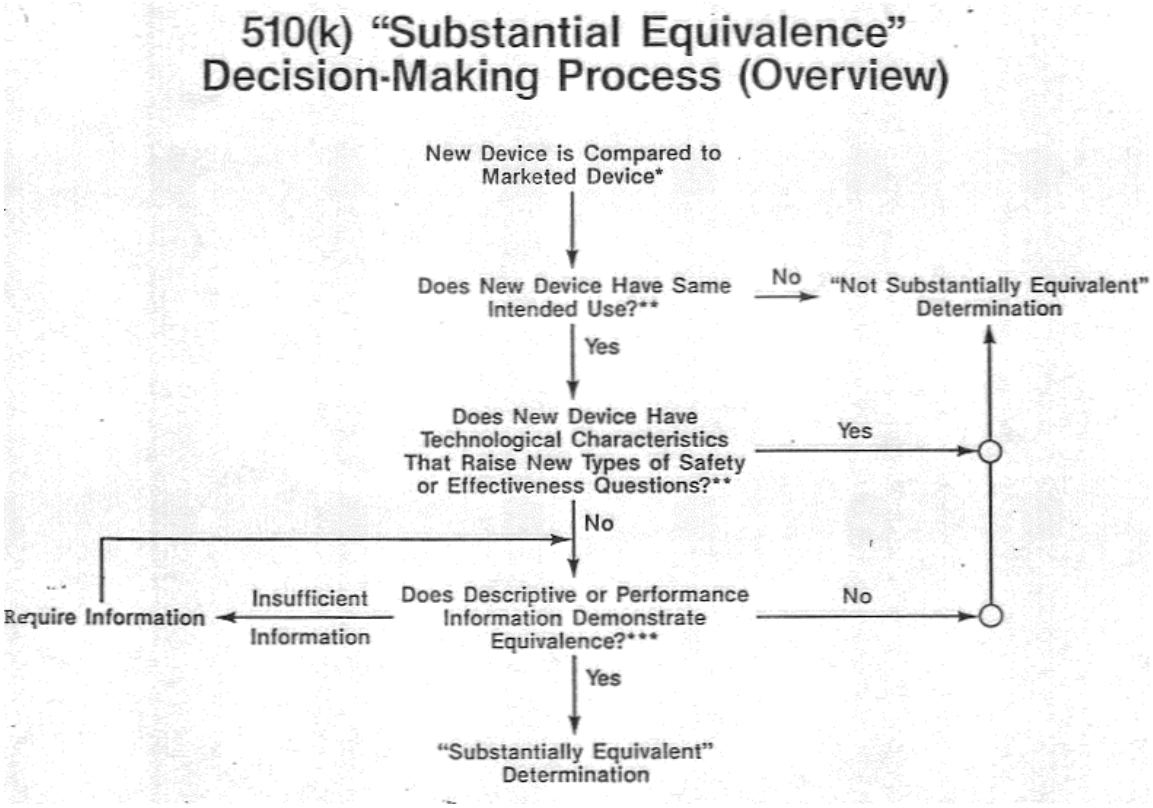
"Thus, from a scientific perspective, to determine which technological changes are consequential, the Center considers whether:

- *the new device poses the same type of questions (emphasis added) about safety or effectiveness as a predicate device.;*
- *there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and*
- *there are data to demonstrate that new technological characteristics have not diminished safety or effectiveness"*

In terms of performance data the guidance notes:

"Typically, 510(k) provides descriptive and testing data that compares the new device to another marketed device within the type, but does not necessarily compare the new device directly to a predicate device. In these cases, the Center can rely, as necessary, on performance data appearing in previously reviewed 510(k) files, in Center classification files, or in the literature, to determine that the device is not only comparable to another marketed device within its type, but is also SE to a predicate device."

The decision tree taken from the guidance and used by FDA and industry for the determination of substantial equivalence and documentation of the decision follows.[33]



d. Significant Changes to 510(k)s Since 1976 Relating to the Determination of Safety and Effectiveness

Based upon my experience and training I believe that the 510(k) review process is robust and truly is a basis for the determination of the safety and effectiveness of medical devices. The process has evolved to increase the requirements for 510(k) submissions in order to establish a device's reasonable assurance of safety and effectiveness. It certainly provides a considerable hurdle to the marketing of new devices.

The first significant change to the act after 1976 regarding 510(k)s was the Safe Medical Device Act of 1990 (SMDA).[34] SMDA increased the authority of FDA and the requirements for manufacturers. The definition of "substantial equivalence" was incorporated into the act, Special

[33] A July 2014 updated chart posted by FDA and used for documentation purposes (http://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf) has essentially the same elements, including the terminology of new "types" of questions regarding technological changes.

[34] The Safe Medical Devices Act of 1990 (P.L. 101-629), which amended the FFD&C Act (21 U.S.C. 201 et seq.), was signed into law on November 28, 1990.

Controls were permitted as a substitute for performance standards for Class II devices, devices could be found equivalent to post-76 legally marketed devices not requiring a PMA, a summary of safety and effectiveness was required, preproduction design controls were now regulated, FDA had to issue a 510(k) equivalence order before a device submitted under a 510(k) could be marketed, and correction and removal reports were required. Also, 510(k)s for Class III devices had to now include a summary of adverse data relating to the safety and effectiveness of the device.

The next change was the FDA Modernization Act of 1997.[35] FDAMA focused FDA resources on those devices presenting the most risk. FDAMA instituted "Good Guidance Practices" to strengthen the development and vetting of documents to the public. The "least burdensome" principles were also added. In a guidance document[36] FDA defined least burdensome as "a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA."

The following change was the Medical Device User Fee Act of 2002. According to FDA, MDUFMA was enacted "in order to provide the Food and Drug Administration (FDA) with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical device manufacturers can bring their safe and effective devices to the American people at an earlier time…"[37]

The 2014 guidance issued by FDA on the determination of substantial equivalence notes "Because devices are classified according to the level of regulatory control necessary to provide a reasonable assurance of safety and effectiveness, classification of a new device through the 510(k) process requires FDA to determine the issues of safety and effectiveness presented by the new device, and the regulatory controls necessary to address those issues."[38]

The guidance goes on to state "The 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate device) differs from the PMA review standard (reasonable assurance of safety and effectiveness). The 510(k) review standard is comparative whereas the PMA standard relies on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."

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[35] FDAMA, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/default.htm.

[36] The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm.

[37] MDUFA, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109149.htm

[38] Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], http://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf .

An Institute of Medicine report of 2011 evaluated the 510(k) program. The IOM report did not contend that a 510(k) review does not make a safety and effectiveness determination.[39] In response to the IOM report FDA CDRH Director, Dr. Jeff Shuren, stated in a press release on July 29, 2011:

> "We appreciate the IOM's report on the 510(k) program, and agree that the public should continue to feel confident in the medical devices on the market today. Medical devices in the U.S. have a strong track record of safety and effectiveness. The 510(k) program has helped support a robust medical device industry in the U.S. and has helped bring lower-risk devices to market for the patients who need them.
>
> FDA believes that the 510(k) process should not be eliminated but we are open to additional proposals and approaches for continued improvement of our device review programs."[40]

6. Postmarket Surveillance, Monitoring Device Experience: Complaints, Medical Devices Reports, Corrective and Preventive Actions

Once a device is marketed FDA continues to monitor its safety and effectiveness. Three FDA regulatory requirements associated with postmarket surveillance, complaint handling, medical device reports, and corrective and preventive action, are closely linked and describe a system for receiving, assessing and taking appropriate action on postmarket signals.

As required by 21 CFR §820.198, Complaint Files, each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that all complaints are processed in a uniform and timely manner, oral complaints are documented upon receipt, and complaints are evaluated to determine whether the complaints represent an event, which is required to be reported to FDA under part 803, Medical Device Reporting.

The manufacturer is required to evaluate complaints and make investigations as needed. Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.

The medical device reporting regulation, 21 CFR §803, establishes the requirements for medical device reporting of events identified in the complaint process for device user facilities, manufacturers, and importers. A manufacturer or importer must report to FDA deaths and serious injuries their device has or may have *"caused or contributed"* to, certain device malfunctions, and they must establish and maintain adverse event files. A manufacturer must also submit specified follow-up.

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[39] Ralph S. Hall and Michelle Mercer, Rethinkng Lohr: Does "SE" Mean Safe and Effective, Substantially Equivalent, or Both? Minn J.L. Sci. & Tech., Vol. 13:2, 2012.

[40] press release, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2011/ucm265908.htm.

The term "caused or contributed" by regulation means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, improper or inadequate design, manufacture, labeling, or user error.[41]

According to FDA, "(MDR) Reports are not required when there is information that would cause a person who is qualified to make a medical judgment (e.g., a physician, risk manager, or biomedical engineer) to reach a reasonable conclusion that a device did not cause or contribute to an MDR reportable event. Information that leads to the conclusion that an event is not reportable must be retained in the MDR event files for the time periods specified in Sec. 803.18."[42]

FDA posts MDRs on the MAUDE database.[43] FDA states on its web site, "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices."

In Subpart J of 21 CFR §820, Corrective and Preventive Action,[44] also known as CAPA, it is required that each manufacturer establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements, in part, for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of product that do not meet a specific requirement (i.e., a nonconformity), or other quality problems.

The manufacturer must investigate the cause of nonconformities relating to product, processes, and the quality system, identify the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems, verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device, implement and record changes in methods and procedures needed to correct and prevent identified quality problems, and ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible.

So, for example, if a complaint is received concerning a death or injury then the manufacturer is obligated to assess it and determine if an investigation is warranted and whether an MDR report must be submitted. Steps may be taken to mitigate the event and/or likelihood of the event reoccurring based on reestablished CAPA procedures. Outputs of decision-making in CAPA may be a recall, labeling changes, notices to users, or other actions.

FDA inspects manufacturers to ensure compliance with 21 CFR §820, including the complaint, MDR and CAPA processes. It uses the Quality System Inspection Technique (QSIT) guidance[45] for FDA investigators as one basis for evaluating these processes.

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[41] 21 CFR §803.3.
[42] FR Notice, Vol.60, No.237 (12/11/95), comment 11.
[43] MAUDE, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM.
[44] 21 CFR §820.100.
[45] http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm.

III. History and Evolution of Surgical Mesh Products for Treatment of Stress Urinary Incontinence (SUI)

A. SUI and Treatment Options

The following is a partial excerpt describing SUI and treatment options on FDA's web site:[46]

> "Stress urinary incontinence (SUI) is a leakage of urine during moments of physical activity that increases abdominal pressure, such as coughing, sneezing, laughing, or exercise. SUI is the most common type of urinary incontinence in women.
>
> SUI can happen when pelvic tissues and muscles, which support the bladder and urethra, become weak and allow the bladder "neck" (where the bladder and urethra intersect) to descend during bursts of physical activity. This descent can prevent the urethra from working properly to control the flow of urine. SUI can also occur when the sphincter muscle that controls the urethra weakens. The weakened sphincter muscle is not able to stop the flow of urine under normal circumstances and when there is an increase in abdominal pressure. Weakness may occur from pregnancy, childbirth, aging, or prior pelvic surgery. Other risk factors for SUI include chronic coughing or straining, obesity and smoking.
>
> It is important for you to consult with your health care provider for proper diagnosis of SUI.
>
> ...
>
> Women have both non-surgical and surgical treatment options to treat SUI…
>
> ...
>
> Surgery to decrease or prevent urine leakage can be done through the vagina or abdomen. The urethra or bladder neck is supported with either stitches alone or with tissue surgically removed from other parts of the body such as the abdominal wall or leg (fascial sling), with tissue from another person (donor tissue) or with material such as surgical mesh (mesh sling).
>
> Surgical mesh in the form of a "sling" (sometimes called "tape") is permanently implanted to support the urethra or bladder neck in order to correct SUI. This is commonly referred to as a "sling procedure."
>
> The use of surgical mesh slings to treat SUI provides a less invasive approach than non-mesh repairs, which require a larger incision in the abdominal wall. The multi-incision sling procedure can be performed using three incisions, in two ways: with one vaginal incision and two lower abdominal incisions,

[46] Stress Urinary Incontinence, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm284109.htm. Viewed on 1/29/16.

called retropubic; or with one vaginal incision and two groin/thigh incisions, called transobturator. There is also a "mini-sling" procedure that utilizes a shorter piece of surgical mesh, which may be done with only one incision."

B. Considerations About Surgical Mesh for SUI

FDA provides the following considerations concerning SUI (emphasis added):[47]

"Mesh sling procedures are currently the most common type of surgery performed to correct SUI. Based on industry estimates, there were approximately 250,000 of these procedures performed in 2010.

While all surgeries for SUI carry some risks, it is important for you to understand the unique risks and benefits for surgical mesh slings used in SUI repair.

In order to better understand the use of surgical mesh slings for SUI and evaluate their safety and effectiveness, the FDA held a panel meeting of scientific experts (Obstetrics and Gynecology Devices Panel of the Medical Device Advisory Committee) in September 2011 and conducted a systematic review of the published scientific literature from 1996 to 2011. For surgical mesh slings used for SUI, both the panel and the FDA's review found that:

- The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year. Longer follow-up data is available in the literature, but there are fewer of these long-term studies compared to studies with one-year follow-up.
- The safety and effectiveness of mini-slings for female SUI have not been adequately demonstrated. Presently, it is unclear how mini-slings compare to multi-incision slings with respect to safety and effectiveness for treating SUI. Additional studies may help the agency to better understand the safety and effectiveness of these devices.
- Mesh sling surgeries for SUI have been reported to be successful in approximately 70 to 80 percent of women at one year, based on women's reports and physical exams. Similar effectiveness outcomes are reported following non-mesh SUI surgeries.
- The use of mesh slings in transvaginal SUI repair introduces a risk not present in traditional non-mesh surgery for SUI repair, which is mesh erosion, also known as extrusion.
- Erosion of mesh slings through the vagina is the most commonly reported mesh-specific complication from SUI surgeries with mesh. The average reported rate of mesh erosion at one year following SUI surgery with mesh is approximately 2 percent. Mesh erosion is sometimes treated successfully with vaginal cream or an office procedure where the exposed piece of mesh is cut. In some cases of

[47] Considerations about Surgical Mesh for SUI, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345219.htm.

mesh erosion, it may be necessary to return to the operating room to remove part or all of the mesh.
- The long-term complications of surgical mesh sling repair for SUI that are reported in the literature are consistent with the adverse events reported to the FDA.
- The complications associated with the use of surgical mesh slings currently on the market for SUI repair are not linked to a single brand of mesh.

The FDA conducted a review of Medical Device Reports (MDRs) received from January 1, 2008 through September 30, 2011. During this time frame the FDA received 1,876 reports of complications associated with surgical mesh devices used to repair SUI. The most common complications reported through MDRs for surgical mesh slings for SUI repair, in descending order of frequency, include: pain, mesh erosion through the vagina (also called exposure, extrusion or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring. Many of these complications require additional medical intervention, and sometimes require surgical treatment and/or hospitalization. With the exception of mesh erosion, the above complications can occur following a non-mesh surgical repair for SUI…

While MDRs are a valuable source of information, this passive surveillance system has notable limitations, including the potential submission of incomplete or inaccurate data, under-reporting of events, lack of denominator data (number of implants), and the lack of report timeliness.

C. Information for Health Care Providers for SUI

The FDA web site includes the following information for health care provides for SUI (emphasis added):[48]

- "Obtain specialized training for each SUI mesh placement technique.
- Be vigilant for potential adverse events from the mesh sling, such as erosion.
- Watch for complications associated with the use of the tools used in transvaginal placement of the mesh sling during the surgical procedure, such as bladder perforations.
- Inform the patient about her choice to have incontinence repair with or without a mesh sling. The patient should understand:
    - the likely success of transvaginal SUI surgery with mesh compared to non-surgical treatment options and non-mesh surgery based on the individual patient factors.
    - the potential postoperative complications of a mesh sling surgery compared to non-mesh surgery and their effect on quality of life.

[48] Recommendations for Health Care Providers, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345221.htm.

- that there is limited information about outcomes after one year.
- whether or not mesh will be used in the repair, and if so, which specific product will be used.
- that a mesh sling is a permanent implant.
- that, as with any SUI surgery, the use of surgical mesh for SUI can make any future surgical repairs more challenging and can put the patient at risk for additional complications and surgeries.

- Ensure that the patient understands the postoperative risks and potential complications of mesh sling surgery.
- Provide patients with a copy of the patient labeling or brochure, if available from the manufacturer"

D. Information for Patients for SUI

The FDA web site contains the following excerpts directed to the patient:[49]

> "Ask your surgeon about all SUI treatment options, including non-surgical options and surgical options that do and do not use mesh slings. It is important for you to understand why your surgeon may be recommending a particular treatment option to treat your SUI.
>
> Any surgery for SUI may put you at risk for complications, including additional surgery."

E. The Development of Surgical Mesh for the Treatment of SUI

The FDA Executive Summary at the September 2011 panel meeting provides a brief overview of the development of surgical mesh for the treatment of SUI and pelvic organ prolapse.[50]

> "Surgical mesh was a pre-amendments device and was classified into Class II (21 CFR 878.3300). Since the 1950s, surgical mesh has been used to repair abdominal hernias. In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair for abdominal repair of POP, and in the 1990s, gynecologists began using surgical mesh for surgical treatment of SUI and vaginal repair of POP. To do so, surgeons would cut the mesh to the desired shape for SUI repair or POP repair and then place the mesh through a corresponding incision. Over time, manufacturers responded to this clinical practice by developing mesh products specifically designed for SUI and POP repair.
>
> In 1996, the Surgical Fabrics (ProteGen Sling) device

[49] Recommendations for Patients, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345230.htm.

[50] FDA Executive Summary, September 8, 2011, OB/Gyn Advisory Committee Meeting, page 5, http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm262488.htm.

manufactured by Boston Scientific Corporation became the first pre-configured surgical mesh product cleared via the 510(k) pathway for surgical treatment of SUI. (The ProteGen Sling was cleared with an indication for "pubourethral support," a phrase which implies an indication for treatment of SUI.) However, use of mesh in SUI repair, referred to as slings or tape, did not become common until after the introduction of the Tension-Free Vaginal Tape (TVT™) System, manufactured by Ethicon/GYNECARE, in 1998. This system was based on the work by Ulmsten and colleagues with the Ethicon Prolene hernia mesh. In 2002, GYNEMESH® PS, also manufactured by Ethicon/GYNECARE, became the first pre-configured surgical mesh product cleared for POP repair.

Over the next few years, surgical mesh products evolved into "kits" that included tools to aid in the delivery/insertion of the mesh. The first kit for SUI repair, the Island Biosurgical Bladder Neck Suspension Kit manufactured by Island Biosurgical, Inc., was cleared in 1997. The first kits for POP repair, the AMS Apogee™ System and the AMS Perigee™ System, both manufactured by American Medical Systems, Inc., were cleared in 2004. Surgical mesh kits continue to evolve in regards to introducer instrumentation, tissue fixation anchors, surgical technique, and incorporation of absorbable materials into the mesh intended to increase material compliance.

The FDA premarket notification review process did not request original clinical studies to support clearance of surgical mesh indicated for treatment of SUI or POP. Attempts to establish clinical effectiveness were undertaken later by the clinical community with clinical trials, published studies, and systematic reviews/meta-analyses. Some of this published literature was incorporated into later 510(k) submissions to support market clearance.

Premarket clearance of surgical mesh indicated for POP and SUI repair was typically based on pre-clinical bench and animal studies as described in the FDA Guidance Document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" issued on March 2, 1999 (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073791.pdf)."

"From 1992-2010, the FDA cleared 168 510(k)s for surgical mesh with urogynecologic indications."

IV. Ethicon TVT Devices

A. Ethicon Gynecare TVT Product Name Variations

Each of Ethicon's TVT devices are known by other project or product names.[51] In this report, the same device may be identified by one of the alternative names. For example:

Name	Some Alternative Names
TVT	TVT Classic TVT Prolene Mesh TVT Standard
TVT-AA	Abdominal Approach TVT Abdominal
TVT-O	TVT Obturator Mulberry
TVT Abbrevo	TVT Twins
TVT Exact	TVT Retropubic Refresh
TVT Secur	TVT-S TVT Universal Mini sling
TVT-D	TVTD

B. Relevant ETHICON Regulatory Submissions

I examined records provided by counsel to help construct a history table of the ETHICON submissions related to TVT. I also did a search of the FDA 510(k) database as referenced in the table to identify additional submissions not included in the records provided by counsel. I ordered the submissions by 510(k) number in the table that follows.

The TVT devices intended to treat stress urinary incontinence are under the surgical mesh classification.

Since PROLENE polypropylene is a key constituent of several of the relevant ETHICON devices its first regulatory submission is important. Catherine Beath testified, "there was a pre-amendment Prolene mesh."[52] A predicate PROLENE polypropylene suture[53] was approved by FDA as a drug under NDA 16-374 and later transitioned to the Center for Devices and Radiological Health as a premarket approval. Eight types of sutures, including PROLENE sutures, were reclassified from Class III to Class II devices under 21 CFR §878.5010,[54] Nonabsorbable polypropylene surgical suture and subject to a special controls guidance document.[55] This suture is referenced as a predicate for the first vaginal tapes and meshes. The history continues with variations of pelvic mesh materials for POP and various vaginal tapes.

[51] DEPO.ETH.MESH.00000067.
[52] Beath deposition, 3/16/12, page 55:16.
[53] see ETHICON submissions table; K940498.
[54] FR Vol.68, Number 106 (Tuesday, June 3, 2003).
[55] www.accessfda.gov.

K Number	Device Name	Material/Change	Predicate	Data
K962530[56] 8/9/96	PROLENE Polypropylene Mesh Nonabsorbable Synthetic Surgical Mesh	Knitted polypropylene identical to PROLENE sutures Additional sizes and key hole shape	PROLENE polypropylene mesh	Bench, preclinical
K972412 9/10/97	ETHICON PROLENE Polypropylene Mesh Hernia Device Nonabsorbable Synthetic Surgical Mesh Implant[57]	PROLENE polypropylene	BARD Marlex mesh PerFix Plug	preclinical
K974098[58] 1/28/98	Tension Free Vaginal Tape (TVT) System	Polypropylene mesh identical to PROLENE polypropylene suture	Protegen Sling[59] PROLENE Suture NDA/PMA 16-374	Bench, preclinical and clinical data
K984220 2/23/1999	PROLENE (Polypropylene) Hernia System[60]	Pre-shaped	PROLENE Hernia System	No data indicated in record
K001122 5/23/2000	PROLENE Soft[61] (polypropylene) nonabsorbable Synthetic Surgical Mesh	Diameter of monofilament and pigmented strands	K962530 and Mersilene mesh (polyester fiber mesh) preamendments	Bench, K962530 preclinical, clinical based on prior Prolene mesh
K002672 11/22/2000	VYPRO Mesh[62]	Mix of polypropylene and polyglactin	PROLENE Mesh and VICRYL (polyglactin 910) Mesh	Bench
K010722 4/27/01	Polypropylene 3D Patch[63]	Three-dimensional	PROLENE Hernia system and Bard Marlex PerFix Plug	Nonclinical laboratory
K012628 10/26/01	GYNECARE[64] Tension-Free Vaginal Tape (TVT) Blue System	Addition of blue pigmented polypropylene fibers interwoven with unpigmented fibers	K974098 K001122	Bench, preclinical, K974098 clinical data
K013718 1/8/2002	GYNEMESH[65] PROLENE Soft Nonabsorbable Synthetic Surgical Mesh for Pelvic Floor Repair	Same as K001122 Pelvic floor claim	K001122 K962530 MERSILENE	K00122 for bench testing, K962530 for preclinical, published literature for clinical
K031925 9/17/03	PROCEED[66] Trilaminate Surgical Mesh	Layers of PS, regular poly, ORC and polydioxanone	PROLENE soft Polypropylene Mesh	Nonclinical and in-vivo testing
K033337	ULTRAPRO Mesh[67]	No FDA info	No FDA info	Animal testing

[56] ETH-02240-02273.
[57] accessdata.fda.gov/cdrh_docs/pdf/K972412.pdf.
[58] 1998 submission, see Attachment.
[59] Removed from market; no effect on other products based on lack of evidence of FDA action.
[60] accessdata.fda.gov/cdrh_docs/pdf/K984220.pdf.
[61] ETH-01646-01818.
[62] accessdata.fda.gov/cdrh_docs/pdf/K002672.pdf.
[63] accessdata.fda.gov/cdrh_docs/pdf/K010722.pdf.
[64] 2001 submission, see Attachment.
[65] ETH00797-00927.
[66] accessdata.fda.gov/cdrh_docs/pdf3/K031925/pdf.

K033568 12/8/03	GYNECARE TVT Obturator Device[68]	New accessories, surgical approach	K974098 K012628 K02356 (sic)	Predicate data
K042603 12/22/04	GYNECARE Prolene Fastener System	Prolene	Mitek meniscal fastener	In-vitro and in-vivo studies
K052401 11/28/05	GYNECARE TVT SECUR System[69]	Material change and needles fixed to implant; change in implantation method	K033568 K012628 K974098	Bench, Preclinical and cadaver data
K060713 5/25/06	PROCEED[70] Surgical Mesh	Change not indicated	PROCEED Trilaminate Mesh	Non indicated
K061533 12/11/06	PROCEED Ventral Patch[71]	Not clear.	PROLENE Soft PROCEED BARD Ventralex VICRYL ETHIBOND	Preclinical, bench and animal
K063562 2/26/07	GYNECARE PROSIMA Pelvic Floor Repair Systems	Precut GYNECARE GYNEMESH PS Mesh Implants and instruments; device balloon assembly; silicon	GYNECARE GYBEMESH PS Nonabsorbable PROLENE Soft Mesh Silimed Vaginal Stent	bench
K070224 4/17/07	ULTRAPRO Plug[72]	Plug and patch	ULTRAPRO mesh BARD Mesh PerFix Plug	Bench and animal
K071249 6/5/07	ULTRAPRO Hernia System[73]	Change in materials	PROLENE hernia system ULTRAPRO mesh	Bench and animal
K071512 5/15/08	GYNECARE PROLIFT Total, Anterior, and Posterior Pelvic Floor Repair Systems GYNECARE PROLIFT+M Total, Anterior, and Posterior Pelvic Floor Repair Systems[74]	PROLIFT: Same as GYNEMESH PS; precut mesh and instruments PROLIFT+M: Same as Ultrapro Mesh; precut mesh and instruments	PROLIFT: K013718 AMS Apogee K040537 AMS Perigee K040623 PROLIFT+M: K033337 Ultrapro Mesh K013718 K040537 K040623	Bench, Cadaver, clinical
K000485 3/16/10	GYNECARE TVT EXACT Continence System[75]	Introducer/needle, handle and trocar change	K904098	Bench testing of new tools
K082216 9/5/08	ETHICON Mesh[76]	Absorbable and nonabsorbable polymers	GYNECARE GYNEMESH PS PROLIFT+M	Functional testing
K093932 4/9/10	ETHICON Physiomesh[77]	Mesh layers, low profile	PROCEED mesh ULTRAPRO Hernia System ULTRAPRO Mesh	Bench and animal

[67] www.fda.gov/ohrms/dockets/ac/08/briefing.
[68] 2003 submission, see Attachment.
[69] 2005 submission, see Attachment.
[70] accessdata.fda.gov/cdrh_docs/pdf6/K060713.pdf.
[71] accessdata.fda.gov/cdrh_docs/pdf6/K061533.
[72] accessdata.fda.gov/cdrh_docs/pdf7/K070224.pdf.
[73] accessdata.fda.gov/cdrh_docs/pdf7/K071249.pdf.
[74] ETH-02015-02238, 01324-01637, 00950-01310, 01903-02014, 01318-01323.
[75] accessdata.fda.gov/cdrh_docs/pdf10/K100485.pdf.
[76] accessdata.fda.gov/cdrh_docs/pdf8/K082216.pdf.
[77] accessdata.fda.gov/cdrh_docs/pdf9/K093932.pdf.

K100485 3/16/10	GYNECARE TVT Exact Continence System[78]	accessory changes	GYNECARE TVT	Trocar tests
K100936 7/1/10	GYNECARE TVT ABBREVO[79]	Change in assembly and accessories	GYNECARE TVT	Bench and cadavers
K113205 6/12/12	ARTISYN Y SHAPED mesh[80]	Y shaped mesh	ALYTE mesh GYNEMESH M RESTORELLE Y	Mechanical testing
K132054 8/23/13	TVT Exact Continence System	FDA summary does not describe change		
K141560 10/23/14 Traditional 510(k)[81]	ETHICON Physiomesh	Macroporous mesh composed of knitted polypropylene, and polydioxanone fibers laminated to absorbable poliglecaprone	K093932 Physiomesh BARD Ventrio Patch Parietex Mesh	Bench testing per guidance, biocompatibility tests, animal implant test

The following is a description of Tension-Free Vaginal Tape (TVT) System from TVT labeling:[82]

DESCRIPTION (System)
TVT consists of the following:
TVT Single-Use Device, provided sterile (available separately)
TVT Reusable Introducer, provided non-sterile (available separately)
TVT Reusable Rigid Catheter Guide, provided non-sterile (available separately)

TVT DEVICE
The TVT device is a sterile single use device, consisting of one piece of undyed or blue (Phtalocyanine blue, Colour index. Number 74160) PROLENE® polypropylene mesh (tape) approximately 1/2 x 18 inches (1.1 x 45 cm), covered by a plastic sheath cut and overlapping in the middle, and held between two stainless steel needles bonded to the mesh and sheath with plastic collars.
PROLENE® polypropylene mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE® polypropylene nonabsorbable surgical suture. The mesh is approximately 0.027 inches (0.7mm) thick. This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use. PROLENE® mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. This bi-directional elastic property allows adaptation to various stresses encountered in the body.

[78] accessdata.fda.gpv/cdrh_docs/pdf10/K100485.pdf.
[79] accessdata.fda.gov/cdrh_docs/pdf10/K100936.pdf.
[80] accessdata.fda.gov/cdrh_docs/pdf/K113205.pdf.
[81] Physiomesh, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K141560.
[82] ETH.MESH.02340484.

V. FDA Public Health Actions Concerning SUI

A. FDA Public Health Notification, October 20, 2008.

FDA issued a Public Health Notification (PHN) on Surgical Mesh, following its examination of adverse events related to various surgical meshes sold by numerous different manufacturers.[83]

The PHN states:

> "This is to alert you to complications associated with transvaginal placement of surgical mesh to treat Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI). Although rare (emphasis added), these complications can have serious consequences. Following is information regarding the adverse events that have been reported to the FDA and recommendations to reduce the risks.
>
> **Nature of the Problem**
>
> Over the past three years, FDA has received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI. These mesh devices are usually placed transvaginally, utilizing tools for minimally invasive placement.
>
> The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia.
>
> Treatment of the various types of complications included additional surgical procedures (some of them to remove the mesh), IV therapy, blood transfusions, and drainage of hematomas or abscesses.
>
> Specific characteristics of patients at increased risk for complications have not been determined. Contributing factors may include the overall health of the patient, the mesh material, the size and shape of the mesh, the surgical technique used, concomitant procedures undertaken (e.g. hysterectomy), and possibly estrogen status.
>
> **Recommendations**
>
> Physicians should:
> - Obtain specialized training for each mesh placement technique, and be aware of its risks.

[83] Public Health Notification, http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm.

- Be vigilant for potential adverse events from the mesh, especially erosion and infection.
- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall (in POP repair).
- Provide patients with a written copy of the patient labeling from the surgical mesh manufacturer, if available."

FDA often provides industry a draft of its public health notice and solicits comments before FDA finalizes the document. Although FDA may consider comments Catherine Beath correctly noted in her testimony "FDA ultimately owns the final version."[84]

B. FDA Safety Communication, July 13, 2011.

On July 13, 2011, FDA issued an updated safety notice concerning serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse but not for SUI.[85]

C. FDA September 2011 Panel Meeting on SUI Devices

The data supporting the safety and effectiveness of TVT was discussed at the September 9, 2011 meeting of the Obstetrics and Gynecological Panel of the Medical Devices Advisory Committee. While all the data presented do not relate solely to ETHICON devices it is important to understand the overall discussions regarding this type of product.

The Transvaginal Mesh Industry Working Group provided a report, dated August 30, 2011, to the Panel and a presentation summarizing the report was given at the panel meeting. ETHICON participated in the creation of the report and presentation to the panel.

The report describes the advances in surgical mesh devices for SUI beginning with use of autologous tissue, xenografts and allografts and associated concerns for their long-term effectiveness, followed by development of synthetic mesh, retropubic and transobturator approaches and single incision slings. The paper notes "patient selection and surgical technique are critical for the success of any surgical procedure…Physicians must be knowledgeable in pelvic floor anatomy and surgery."

The Group reviewed MDR reports. As noted, "This review of the overall MDR rate, as well as rates associated with serious adverse events

[84] Beath deposition, 3/6/12, page 261:24-25.
[85] http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm.

(SAE), indicated that while there was an increase in adverse events overall, the rate remains low with an average rate of 0.13% for the 2008 to 2010 period. When comparing the number of serious adverse events to the total adverse events for each time period, it was determined that the 2005 to 2007 period had a 33% rate of SAE/Total AE (0.02%SAE) and 2008 to 2010 had a rate of 31% (0.04% SAE). Therefore, the ratio between serious adverse events and total adverse events has remained constant between the two time periods. While the Working Group analysis is still saddled with many of the limitations of the MAUDE database itself, the usefulness of the denominator information allows a better analysis of the change in event rates."

The Group assessed the clinical literature, adverse effects and effectiveness, summarized in appendices to the report, noting "There is strong evidence available to date that demonstrates that the midurethral sling has a favorable benefit/risk profile and that these procedures are valuable treatment options for women suffering from SUI. The risk and benefit is well characterized and understood by the clinical community."

The FDA Executive Summary provided to the panel for the meeting makes states:[86]

> "The FDA did not request original clinical performance data for either the first generation minimally invasive suburethral slings or the single-incision mini-slings. A substantial number of quality clinical trials, as well as systematic reviews, have been published for the first generation minimally invasive slings that provide evidence of safety and effectiveness of these devices."

Based on its assessment of the available safety and effectiveness data FDA reported the following conclusions:

> "After considering all available data on both safety and effectiveness, and considering the risk/benefit profile, it appears that new premarket clinical trials are not warranted for minimally invasive slings for SUI unless the device has new features (e.g. new polymer or coating) that could affect device performance. The FDA recognizes, however, that the strength of this conclusion is limited by what is largely short duration (2 years) follow-up in the literature with limited data available past 3 years of follow-up.
>
> The FDA believes that new clinical performance data are needed in the premarket setting to ensure the safety and effectiveness of the second generation synthetic slings or "single incision mini slings." The FDA's position is based on the small number of non-randomized studies and two randomized controlled studies which suggest that mini slings may be less effective compared to the first generation minimally invasive synthetic slings. Preliminary safety outcomes suggest that the mini-sling may be associated with greater intraoperative blood loss and lead to higher rates

[86] FDA Executive Summary, September 9, 2011, OB/Gyn Advisory Committee Meeting, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM270402.pdf.

> of vaginal mesh erosion compared to first generation slings. Although future randomized controlled trials may lead to different conclusions, the FDA believes that premarket performance data are needed at this time to support market clearance of the second generation synthetic slings.
>
> The regulatory threshold for the FDA to request clinical outcomes data is different for the premarket setting compared to the postmarket setting. The FDA believes that whereas the published literature provides sufficient clinical performance data to support new premarket notifications for the first generation SUI sling, it may be appropriate to require special postmarket surveillance studies to improve the FDA's understanding of the safety profile of all types of minimally invasive slings (including mini-slings).
>
> Finally, the FDA recognizes that all minimally invasive synthetic slings (including mini-slings) are associated with risk of failure as well as patient injury. The FDA believes, however, that the peer reviewedliterature affords sufficient understanding of the nature and severity of risks from minimally invasivesynthetic slings to enable FDA to review these devices under the Special Controls provisions of 510(k) premarket notification as Class II medical devices. The FDA is not proposing to reclassify these devices from Class II to Class III (Premarket Approval)."

The Panel concluded the following:[87]

> Question 1 retropubic and transobturator suburethral slings
>
> The panel consensus was that the safety and effectiveness of these devices is well-established. Unless there are significant material changes or changes in the surgical access (including introducer instrumentation), premarket clinical studies would generally not be necessary. The panel consensus was that consideration should be made to better characterize low frequency life-altering adverse events, potentially via collaboration with industry and use of existing large-scale health databases. The panel did not believe that 522 postmarket studies would be an appropriate mechanism for this, and the consensus was that 522 postmarket studies for these devices are not necessary.
>
> Question 2 single-incision mini-slings
>
> The panel consensus was that the safety and effectiveness of mini-slings is not well understood and that premarket evaluation of new mini-slings should be supported by clinical studies. Such studies should have a control arm of women using a retropubic or transobturator sling with a well-understood risk-benefit profile. The panel believed that the FDA could address this using the 510(k) premarket notification pathway.

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[87] 24 hour memo, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM271769.pdf.

> The panel consensus also was that, in this case, 522 postmarket studies should address the safety and effectiveness of currently marketed mini-slings. In such 522 studies, the currently marketed mini-sling should be compared to a conventional retropubic or transobturator sling with either a randomized or rigorous cohort design and a 3-5 year follow-up.

D. March 2013 update to FDA website concerning SUI

As noted on FDA's website, on March 27, 2013, the FDA updated the Urogynecologic Surgical Mesh Implant website to include more information for patients about stress urinary incontinence (SUI). This update provides the FDA's current thinking about the use of surgical mesh for repair of SUI and is based on an analysis of adverse events reported to the FDA, findings reported in the scientific literature and input received from the Sept. 9, 2011 meeting of the Obstetrics and Gynecology Devices Panel of the Medical Device Advisory Committee. Additionally, the FDA is following through on our commitment to inform the public about surgical mesh for stress urinary incontinence (SUI).

E. FDA Reclassifies Only Surgical Mesh Only for Pelvic Organ Prolapse Repair in 2016

On May 21, 2014, FDA published a proposal to reclassify surgical mesh for transvaginal pelvic organ prolapse (POP) repair from Class II to Class III.[88] FDA also proposed to reclassify "specialized" urogynecological surgical mesh instrumentation from Class I to Class II. The FDA proposed order states the mesh reclassification does not include surgical mesh indicated for surgical treatment of stress urinary incontinence, sacrocolpopexy (transabdominal POP repair), hernia repair, and other non-urogynecologic indications. The proposal includes entirely new classification regulations for mesh used in POP repair and for the specialized urogynecological instruments. In January 2016, FDA finalized this proposal.[89]

F. Section 522 Orders

Postmarket surveillance under section 522 of the Federal Food, Drug, and Cosmetic Act (the act) is one means by which the Food and Drug Administration (FDA) can obtain additional safety and/or effectiveness data for a device after it has been cleared through the premarket notification (510(k)) process.

On January 3, 2012 FDA issued 522 postmarket study orders to various mesh manufacturers, including five orders to ETHICON for specific surgical mesh products: GYNEMESH PS, PROLIFT, PROLIFT +M, Prosima and

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[88] FDA proposed reclassification of POP mesh, and instruments for POP and SUI, https://www.federalregister.gov/articles/2014/05/01/2014-09907/reclassification-of-surgical-mesh-for-transvaginal-pelvic-organ-prolapse-repair-and-surgical.

[89] 81 FR 353.

TVT Secur.[90] The orders requested postmarket surveillance studies and specified the questions to be answered by the studies and elements of the study protocols.[91] Notably, FDA did not issue any such orders with respect to TVT.

VI. Post Panel FDA Action Not Taken on TVT Classic; Professional Associations and UK National Institute Support the Safety and Effectiveness of Full-Length/Suburethral/TVT Vaginal Slings

After the 2011 FDA panel proceedings on SUI the actions taken by FDA and statements of professional societies and the UK indicate support for midurethral slings for treatment of SUI.

A. FDA Issued no additional special controls for TVT

The FDA has never issued any postmarket study order for Gynecare TVT (TVT Classic) and this device has remained on the market for the last 15 years. FDA has posted information for patients and providers, which I discuss above in this report.

B. January 2014 American Urogynecological Society (AUGS) and Society of Urodynamics, Female Pelvic Medicine and Urogential Reconstruction (SUFU) Statement

On January 7, 2014, AUGS posted a statement entitled "Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence."[92] The statement reads " The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women." Furthermore it states the following:

> "Polypropylene material is safe and effective as an implant."
>
> "The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history."
>
> "Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients."
>
> "The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI."

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[90] 522 study listing, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm?start_search=E#E.
[91] ETH.MESH.030467737-030467740.
[92] http://www.augs.org/p/bl/et/blogid=16&blogaid=194.

On March 24, 2014 AUGS and SUFU posted two related documents, one concerning Frequently Asked Questions by Patients: Mid-urethral slings for Stress Urinary Incontinence and another for Providers.[93] The statements read, in part:

> "The mid-urethral sling is considered safe and effective by the US Food and Drug Administration (FDA). As with any surgery, complications can occur but they are typically minor and can usually be repaired."
>
> "A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of mid-urethral slings as a treatment for SUI [1]."
>
> "The difficulties and complications associated with mid-urethral slings are similar in character to that seen with non-mesh procedures (bladder outlet obstruction, urinary tract injury, dyspareunia, pain, etc.) with the exception of vaginal mesh exposure and mesh perforations into the urinary tract."
>
> "As an implant for the surgical treatment of SUI, macroporous, monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years [5]."
>
> "Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants."

C. March 2013 AUGS Statement

On March 26, 2013, the AUGS published a statement entitled "Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders."[94] It reads "The American Urogynecologic Society strongly opposes any restrictions by state or local medical organizations, healthcare systems, or insurance companies which ban currently available surgical options performed by qualified and credentialed surgeons on appropriately informed patients with pelvic floor disorders….Our Justification for this position statement is described below. (parts of justification noted below)

1. A complete restriction on the use of surgical mesh was not the stated intent of the FDA safety communication.

2. The decision on surgical alternatives should be made by the patient and her surgeon.

3. A ban on surgical mesh would prohibit the surgical studies mandated by the FDA and recommended by the NIH, ACOG, and AUGS.

4. In some circumstances transvaginal mesh for pelvic organ prolapse may be the most appropriate surgical option.

5. Any restriction of mesh slings for the treatment of stress urinary incontinence is clearly not supported by any professional organization or the FDA.

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[93] Id.

[94] http://www.augs.org/p/bl/et/blogid=6&blogaid=160.

However, it is particularly important to note that full-length midurethral slings were excluded from the (FDA) mandated post marketing studies. In a recent study involving 53 expert urologists and urogynecologists (of whom >90% were fellowship trained) and who could select among many surgical options, the full-length synthetic midurethral sling was the preferred opinion in 93% for the surgical treatment of primary stress incontinence. Full length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard of care for stress urinary incontinence surgery.

6. Any restriction of mesh placed abdominally for the treatment of prolapse is clearly not supported by any professional organization or the FDA.

7. Instead of a ban on mesh we recommend the implementation of credentialing guidelines so that mesh procedures are performed by qualified surgeons.

D. November 2011 American Urologic Association (AUA) Statement

In November 2011 AUA published a position statement regarding the use of vaginal mesh for the surgical treatment of stress urinary incontinence. It states:[95]

> Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI.
>
> Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques. The AUA Guideline also indicates that intra-operative cystoscopy should be performed during all synthetic sling procedures to identify urinary tract injury.

[95] nihttp://www.auanet.org.

> The AUA strongly agrees with the FDA that a thorough informed consent should be conducted prior to synthetic sling surgery. The AUA also agrees that surgeons who wish to perform synthetic sling surgery should:
> • Undergo rigorous training in the principles of pelvic anatomy and pelvic surgery.
> • Be properly trained in specific sling techniques.
> • Be able to recognize and manage complications associated with synthetic mesh sling placement.

E. National Institute for Health and Care Excellent (NICE); Urinary Incontinence: The management of urinary incontinence in women[96]

The National Institute for Health and Care Excellence (NICE) provides national guidance and advice in the UK to improve health and social care. The September 2013 NICE guidance on treatment of urinary incontinence states the following regarding synthetic tapes:

> When offering a synthetic mid-urethral tape procedure, surgeons should: use procedures and devices for which there is current high quality evidence of efficacy and safety…use a device manufactured from type 1 macroporous polypropylene tape…The guideline only recommends the use of tapes with proven efficacy based on robust RCT evidence (emphasis added). However, technological advances are frequent, therefore the choice of tape should include devices that are shown in future clinical trials to have equal or improved efficacy at equal or lower cost. At the time of publication (September 2013) the following met the Guideline Development Group criteria… TVT or Advantage for a "bottom-up retropubic approach.

The guideline does not recommend culposuspension or types of biological slings for the treatment of stress UI. It also provides long-term outcome data to aid the physician in informing their patients.

F. March 2014 Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG) Statement

In March 2014 RANZCOG published a position statement on midurethral slings.[97] The statement reads:

> "Mid-urethral slings are minimally invasive procedures developed in the early 1990s to treat female stress urinary incontinence. These slings are narrow, synthetic polypropylene tapes that are surgically placed beneath the middle part of the urethra (water pipe) to provide dynamic support to stop leakage from the bladder. They have been shown to be as effective as more invasive traditional surgery with major advantages of shorter operating and admission times, and a quicker return to normal activities, together with lower rates of complications.[3] This has resulted in MUS becoming the operation of choice in Europe, the United

[96] NICE guideline: http://guidance.nice.org.uk/CG171/NICEGuidance/pdf/English.
[97] www.ranzcog.edu.au.

Kingdom, Australasia[4] and the USA[5] for treatment of SUI.

The USA Food and Drug Administration (FDA) released a white paper[6] and safety communications[7] regarding safety and effectiveness of transvaginal placement of surgical mesh specifically for pelvic organ prolapse. A prolapse is where some of the pelvic organs bulge downwards giving rise to symptoms of an uncomfortable vaginal lump. Media attention[8] on this totally distinct and separate issue of mesh use in women has the potential to cause unnecessary confusion and fear in women considering MUS for treatment of stress urinary incontinence. Both RANZCOG and UGSA wish to strongly emphasise that the US FDA publications clearly state that MUS were not the subject of their safety communication.

There is robust evidence[9-11] to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use. These scientific publications studied all types of patients, including those with co-morbidities such as prolapse, obesity and other types of bladder dysfunction. It is, however, acknowledged that any operation can cause complications and for MUS, these include bleeding, damage to the bladder and voiding difficulties[12]. Nevertheless, the results of a recent large multi-centre trial[13] have again confirmed the excellent outcomes and low risks of complications to be expected after treatment with MUS. Additionally, long term effectiveness has been demonstrated in studies following patients for up to 17 years.[14-15] In Australia, it has been the operation of choice to treat for female SUI since 2004. RANZCOG and UGSA support the use of monofilament polypropylene mid-urethral sling for surgical treatment of female stress urinary incontinence."

G. January and March 2014 AUGS-Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) Statement

On January 3, 2014, AUGS-SUFU published a joint notice entitled "Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence."[98] The statement reads, in part, as follows:

> ***The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women.***
>
> **Introduction**
>
> The purpose of this position statement by the American Urogynecologic Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) is to support the use of the midurethral sling in the surgical management of stress urinary incontinence, the type of urine leakage generally associated with coughing, laughing and sneezing.

[98] http://sufuorg.com/docs/news/AUGS-SUFU-MUS-Position-Statement-APPROVED-1-3-2014.aspx.

Developed in the early 1990's, midurethral slings (MUS) treat stress urinary incontinence (SUI) in a minimally invasive, generally outpatient procedure. This technique utilizes a small mesh strip composed of monofilament polypropylene placed through the vagina under the mid-urethra exiting from 2 small sites in either the suprapubic or groin areas.
SUI is a highly prevalent condition of involuntary urine leakage resulting from faulty closure of the urethra typically associated with coughing, sneezing or exertion. SUI is often a debilitating and bothersome condition that can substantially reduce a woman's quality of life. Although non-surgical treatments such as pelvic floor exercises and behavioral modification are helpful in alleviating symptoms in some women [1], many proceed with surgery which is a more effective treatment [2].

In July 2011, the U.S. Food and Drug Administration (FDA) released a white paper [3] and safety communication [4] on the safety and effectiveness of transvaginal placement of surgical mesh specifically for pelvic organ prolapse. In addition, lawyers have publicly advertised their services, targeting women with transvaginal mesh placed for both pelvic organ prolapse and stress urinary incontinence (SUI), and the media has reported on the pelvic organ prolapse mesh litigation. We are concerned that the multimedia attention has resulted in confusion, fear, and an unbalanced negative perception regarding the midurethral sling as a treatment for SUI. This negative perception of the MUS is not shared by the medical community and the overwhelming majority of women who have been satisfied with their MUS. Furthermore, the FDA website states that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year."[5].

Justification for the Position Statement
1. Polypropylene material is safe and effective as a surgical implant.

Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years [8].

2. The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history.

A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI [9]. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific

evidence in the peer reviewed scientific literature [9]. The MUS has been studied in virtually all types of patients, with and without comorbidities, and all types of SUI. Multiple randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently demonstrated its clinical effectiveness [9-12] and patient satisfaction [12]. Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy [8]. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

3. Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.

Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery [13]. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members [14].

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.

The midurethral sling was not the subject of the 2011 FDA Safety Communication, "*Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Vaginal Placement for Pelvic Organ Prolapse*."[3]. In this document, it was explicitly stated: "The FDA continues to evaluate the effects of using surgical mesh for the treatment of SUI and will report about that usage at a later date." In 2013, the FDA website stated clearly that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year." [5]

Conclusion

The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. One of the unintended consequences of this polypropylene mesh controversy has been to keep women from receiving any treatment for SUI. This

> procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence.

On March 24, 2014 AUGS and SUFU posted two related documents, one concerning Frequently Asked Questions by Patients: Mid-urethral slings for Stress Urinary Incontinence and another for Providers.[99] The statements read, in part:

> "The mid-urethral sling is considered safe and effective by the US Food and Drug Administration (FDA). As with any surgery, complications can occur but they are typically minor and can usually be repaired."
>
> "A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of mid-urethral slings as a treatment for SUI [1]."
>
> "The difficulties and complications associated with mid-urethral slings are similar in character to that seen with non-mesh procedures (bladder outlet obstruction, urinary tract injury, dyspareunia, pain, etc.) with the exception of vaginal mesh exposure and mesh perforations into the urinary tract."
>
> "As an implant for the surgical treatment of SUI, macroporous, monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years [5]."
>
> "Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants."

I. November 2015 ACOG/AUGS Practice Bulletin

A November 2015 ACOG/AUGS Practice Bulleting states the following regarding midurethral slings:[100]

[99] Id.
[100] Number 155, November 2015.

Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.

There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.

. . .

Synthetic midurethral mesh slings are the most common primary surgical treatment for stress urinary incontinence in women (67). Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension (68–70). Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings (68). Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings (69). For these reasons, midurethral synthetic mesh slings have become the primary surgical treatment for stress urinary incontinence in women (67, 71). However, in women who decline or are not candidates for synthetic mesh slings, autologous fascial bladder neck slings and Burch colposuspension (laparoscopic or open) remain effective treatment options.

Although controversy exists about the role of synthetic mesh used in the vaginal repair of pelvic organ prolapse, there are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women. For this reason, and to clarify uncertainty for patients and practitioners, the American Urogynecologic Society and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction published a position statement recognizing polypropylene mesh midurethral slings as the "standard of care" in the surgical treatment of stress urinary incontinence (72).

Although there are many ways to place midurethral slings, the main approaches used are retropubic and transobturator techniques. Evidence from a 2015 systematic review demonstrates that these approaches are effective and appear to be comparable in terms of efficacy and patient satisfaction (73). Subjective cure rates up to 1 year after surgery were similar and ranged from 62% to 98% (transobturator route) and 71% to 97% (retropubic route). Short-term objective and long-term (more than 5 years) subjective and objective cure rates also were similar. Voiding dysfunction, bladder perforation, major vascular or visceral injury, and operative blood loss were more common with retropubic slings, whereas groin pain was more common with transobturator slings. Mesh complications (eg, exposures, erosions) were uncommon and did not differ between routes of sling placement (2% overall).

Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.

There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.

VII. Opinions

In forming my opinions, I employed methodologies consistently used by health care companies and regulatory authorities to address and evaluate premarket data, post-approval safety data, risk reduction strategies and labeling obligations. These methods are also consistent with those utilized by me, the sole member of Ulatowski Consulting, LLC, in the conduct of my assignments with both U.S. and international health care clients manufacturing medical devices including preparation of regulatory submissions and post-market efforts, preparation of regulatory and scientific protocols, labeling and other risk mitigation evaluations. My opinions are also predicated upon the Food, Drug, and Cosmetic Act, my numerous interactions with the Federal Trade Commission on device labeling and promotion, the Code of Federal Regulations, Federal Registers, and industry practices and standards.

My participation in this litigation and the development of the opinions enclosed herein follow an extensive review process. As described earlier, I possess extensive experience in the medical device industry

and draw on this experience in conducting my tasks under the auspices of Ulatowski Consulting, LLC, including the reviews provided herein.

As described, I have performed a thorough and integrated review of the publicly available information and regulatory documents, including those produced during discovery, identified in this report and listed in Exhibit B. I analyzed those documents for their relevance. The employed methodology also included a review of the production documents, depositions/transcripts, and other materials provided to me by Counsel, or requested by me from Counsel. Upon retrieval, receipt, and review I considered documents for possible inclusion in the evaluation for this report. If additional relevant proprietary documentation was required, and I was unable to independently locate this data/information, I made a request of Counsel for any related documents to be reviewed by me. I analyzed these documents for their regulatory relevance and conformity to industry practices and standards in forming my opinions in the same manner I would have assessed them when I was a premarket evaluator or the chief medical device compliance officer at FDA, and also in the same way I would evaluate them in my current capacity as a consultant to companies on medical device regulatory aspects.

The employed methods also include my reviews of depositions, corresponding exhibits, potentially associated with regulatory affairs, post-market surveillance, device design and manufacturing, and medical services, among others. Reviews of depositions and exhibits are critical. Because I have been engaged in all the aspects of medical device design, development and commercialization, I can interpret and evaluate industry testimony.

Based upon my analysis of these documents and information, as well as my experience, knowledge, and training, I have formed opinions with regard to the Ethicon TVT Classic. Each of the opinions set forth below is held to a reasonable degree of scientific and regulatory certainty. My prior testimony is listed in Exhibit C. I have no publications in the past 10 years.

I may use visual aids or demonstrative exhibits, such as diagrams, images, slides or charts, to illustrate and or explain my opinions and analyses in this report, as well as excerpts, charts, and other information from the materials I have cited in my report or identified in the materials reviewed.

I reserve the right to supplement this report and my opinions as discovery progresses in this case.

1. It is my opinion that the recall of the Microvasive ProteGen Sling, one of the predicates for the TVT Classic, had no regulatory or safety impact whatsoever on the continued marketing of the TVT Classic. It was appropriate and consistent with industry standards for Ethicon to use ProteGen as a predicate.

The cleared 510(k) for the Ethicon Tension Free Vaginal Tape (TVT) System, also known as TVT Classic, included the ProteGen Sling, manufactured by Microvasive, a Boston Scientific Company, as one of the

predicates for the Ethicon TVT device.[101] The Ethicon TVT System and the ProteGen Sling were similar in that they had the same intended use, clinical mechanism to achieve continence and insertion site, i.e., pubourethral sling to treat stress urinary incontinence by urethral support with incision on the anterior vaginal wall. They also used accessory devices and required anesthesia.

The Ethicon TVT System was different from the ProteGen Sling in several important respects. The material for the Ethicon TVT device is knitted filaments of polypropylene (Prolene) while the ProteGen Sling consisted of woven polyester impregnated with collagen. The collagen ingredient was absorbable. The Ethicon device utilized fixation through the skin while the ProteGen Sling used sutures anchored to bone.

FDA states the following regarding the ProteGen Sling in its Executive Summary to the Obstetrics and Gynecological Devices Advisory Committee on September 9, 2011:[102]

> In 1996, the Surgical Fabrics (ProteGen Sling) device manufactured by Boston Scientific Corporation became the first pre-configured surgical mesh product cleared via the 510(k) pathway for surgical treatment of SUI. (The ProteGen Sling was cleared with an indication for "pubourethral support," a phrase which implies an indication for treatment of SUI.)

Boston Scientific/Microvasive reportedly recalled the ProteGen Sling in January 1999.[103]

Microvasive's voluntary recall of the ProteGen Sling, the sling predicate for the Ethicon TVT System, did not have a regulatory or safety impact on the Ethicon TVT System.[104] The safety impact is most important. In my opinion although the ProteGen Sling and the Ethicon TVT device were substantially equivalence by the FDA regulatory standard they were sufficiently different in materials and anchoring to disassociate the ProteGen experience from that of the Ethicon TVT. Also, the post market clinical evidence for the Ethicon TVT device in January 1999 when the ProteGen Sling was recalled and later was demonstrating that the Ethicon TVT device was performing as intended.[105] The 510(k) for the Ethicon TVT System included clinical evidence attesting to its safety and effectiveness.[106] Therefore, there was no safety basis for a recall of the TVT device in January 1999.

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[101] ETH.MESH.00371539-00371542.
[102] FDA Executive Summary, http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/obstetricsandgynecologydevices/ucm270402.pdf
[103] FDA public records of recalls do not extend to 1999. A statement of the status of ProteGen is contained in various publications, e.g., Erosion of Woven Polyester Pubourethral Sling, December 1999, http://www.ncbi.nlm.nih.gov/pubmed/10569572.
[104] ETH.MESH.00371496-00371497.
[105] Dr. David Robinson, a medical director at Ethicon, began using the TVT device shortly after it became available. He testified, "Eventually the TVT became the gold standard." Robinson deposition, 7/24/13, Page 45:10-11.
[106] Id., TVT System 510(k).

Based on the lack of a safety issue, FDA would not have had a regulatory basis to take administrative action on the TVT Classic 510(k). There is no explicit statutory authority or regulation on vacating a determination of substantial equivalence, or a regulatory method for FDA to rescind a 510(k) determination of substantial equivalence. However, a ruling of a US District Court gives credence to FDA's position that it has the authority to rescind a 510(k), albeit as the court opined in "rare situations" so long as FDA acts in a "reasonable time." [107,108]

FDA has employed an administrative procedure for rescission but the criterion for rescission by this administrative procedure when the ProteGen was recalled was not applicable to the Ethicon TVT System. Based on my experience, the criterion for rescission was submission by the applicant of incorrect information. An FDA administrative process for rescission of a 510(k) was in a proposed rule that never went final.[109] The expanded rescission criteria in the proposed rule were "information in the 510(k) is incorrect, incomplete, unreliable, or not evaluated properly by FDA in accordance with section 513(f) and (i) of the act." I conclude from my review of the Ethicon TVT System 510(k)[110] that none of these expanded criteria applied to the Ethicon 510(k).

FDA took no public action to rescind any sling device relying on the ProteGen Sling as a predicate. FDA did not use any other statutory and regulatory remedy at its disposal to remove any Ethicon TVT device from the marketplace due to the recall of the ProteGen Sling. Indeed, FDA cleared several additional Ethicon slings after the ProteGen recall, including, for example, TVT-AA, TVT-O, TVT-Secur, TVT Abbrevo and TVT Exact (see Section IV.B. above for 510(k) listing).

2. It is my opinion that the primary material used in the Ethicon TVT device, Prolene, is safe and effective from a regulatory perspective; long-term safe and effective performance of the material supports its continued regulatory acceptance as an implantable material. It is also consistent with industry standards and practices for Ethicon to use Prolene as the material for surgical mesh.

Materials are selected for use in medical devices based on the safety and performance requirements of the finished device. Biocompatibility, engineering and preclinical performance are important industry standards considered. Ultimately the safety and performance of a material in a finished device is demonstrated over the course of its clinical usage.

PROLENE is the primary material used in the TVT Classic. FDA has a long history and extensive knowledge of the safe and effective performance of PROLENE. PROLENE Polypropylene Suture (Nonabsorbable Surgical Suture USP, Type B) was regulated by FDA as a drug prior to the enactment of

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[107] FDA has considered a future statutory amendment to provide authority for rescission. See "Plan of Action for Implementation of 510(k) and Science Recommendations", http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm239450.pdf.

[108] Ivy Sports Medicine, LLC v. Sebellius et al., No 11-cv-1006.

[109] 66 FR 3523, 3525 (January 16, 2001).

[110] TVT System 510(k), K974098, ETH.MESH.00371496-00371594.

the medical device amendments to the Federal Food, Drug and Cosmetic Act. FDA approved a New Drug Application, NDA 16-374, for the Ethicon PROLENE Suture (monofilamentous dyed and undyed) on April 16, 1969.[111] FDA determined that the PROLENE suture was safe and effective. The original NDA file for the Ethicon PROLENE Suture and subsequent submissions, consisting of supplements, amendments and annual reports, is extensive.[112] The original basis for approval was extensive chemistry, preclinical and clinical information.

FDA approved the final labeling in 1988 and numerous supplements to the Prolene suture NDA. The FDA-approved 1988 label included warnings of a "minimal, transient acute inflammatory reaction" and that the material "resists involvement in infection."

PROLENE sutures transitioned to PMA regulations when the product was transferred to the medical device center in FDA. Based upon my 37 years of experience coordinating and evaluating regulated products in both the drug and medical device Centers in FDA the PROLENE Suture NDA file, it is my opinion that the PROLENE suture PMA is a comprehensive compilation of medical and scientific evidence supporting FDA's original and continued determination that the PROLENE Suture, indeed the PROLENE material, is safe and effective.

Ethicon continued to comply with NDA/PMA reporting requirements until those NDA/PMA requirements were transformed to 510(k) requirements by the reclassification of nonabsorbable polypropylene surgical sutures from Class III to Class II.[113] Down classification of PROLENE sutures from Class III to Class II is an important indicator that FDA and its panel of advisors believed that there was sufficient valid scientific evidence of the safety and effectiveness of the PROLENE sutures to demonstrate Class II controls were adequate for PROLENE sutures.

In addition to the suture as a foundation of the long-term safety and effectiveness of PROLENE, Catherine Beath testified, "there was a pre-amendment PROLENE mesh."[114] This preamendments PROLENE mesh was described in K962530, the submission for a modified PROLENE mesh.[115]

The AUGS statement noted in Section VI above states the following:

PROLENE is the primary component in all Ethicon transvaginal tapes including, for example, the TVT Classic, the TVT-O[116] and TVT-Secur.[117] For FDA classification purposes these tapes are generically grouped under the General and Plastic Surgery classification regulation Surgical Mesh, 21 CFR §878.3300 as Class II devices. When FDA proposed

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[111] ETH.MESH.09625731-09625737.
[112] Original submission January 17, 1966 supported by IND 1688, 4 original volumes ETH.MESH.00019840-00019846. Subsequent submissions to FDA comprise nearly 50 primary volumes.
[113] ETH.MESH.09634662-09634663.
[114] Beath deposition, 3/26/2012, page 55:16.
[115] ETH-02240-73. Preamendments devices are those that were marketed prior to the enactment of the 1976 medical device amendments to the Act, and also were not subject to regulation as drugs prior to 1976.

[116] Comparison of TVT Classic to TVT-O, ETH.MESH.08108658.
[117] Ingredients of TVT Secur, ETH.MESH.01311888.

the classification of the preamendments surgical mesh in 1982[118] it considered the recommendations of the General and Plastic Surgery, Orthopedic, and Gastroenterology and Urology Device Panels. The Panels relied upon their clinical experience, clinical data and risks to health when evaluating and classifying preamendments surgical mesh. FDA finalized the classification in 1988.[119]

1. Polypropylene material is safe and effective as a surgical implant.

Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years [8].

Mr. Gregory R. Jones, Director of Regulatory Affairs when the TVT Classic was first marketed, testified regarding the 510(k) submission of TVT to FDA:[120] PROLENE mesh is well-known, well understood, been on the market for quite some time. PROLENE sutures had been on the market and well-known and well understood. The testing that had been done over the years on PROLENE Suture and PROLENE Mesh was pretty extensive." I agree with his statement. PROLENE mesh has been on the market now for approximately 40 years and FDA has taken no action to remove products from the market on the basis of any of them containing this material.

I find no evidence in the PROLENE Suture NDA file or on FDA's web site of any adverse regulatory action taken by FDA or any recall focused on any aspect of safety or effectiveness of the PROLENE material.[121]

In sum, from a regulatory perspective Ethicon submitted ample data over the years to demonstrate that is a safe and effective material for implantable use. FDA and its panel of experts have reconfirmed this finding in reaching all their decisions on classification, reclassification, approvals and clearances of new PROLENE containing devices. Clinical experts confirm the safety and effectiveness of PROLENE.

3. It is my opinion that a change in material or PROLENE weave specifications for the TVT Classic would require the submission of a new 510(k) to FDA and clearance by FDA before the modified device could be marketed.

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[118] 47 FR 2810 (January 19, 1982).
[119] 53 FR 23856 (June 24, 1988).
[120] Jones deposition, 8/20/13, page 185:19-25.
[121] Recall activities included, for example, instances of counterfeit sutures.

The composition of the TVT Classic mesh, as described in the original Ethicon 510(k) cleared by FDA on January 28, 1998, is "knitted filaments of extended polypropylene identical in composition to that used in PROLENE polypropylene suture (Ref. NDA/PMA #16-374).[122] Ethicon also stated to FDA that the polypropylene strands used to fabricate PROLENE mesh are the same strands used to fabricate PROLENE polypropylene Nonabsorbable Surgical Suture.[123] Dan Smith, currently an engineering fellow at Ethicon, testified that since the clearance of TVT Classic one clear PROLENE fiber in the mesh construction was replaced with a blue PROLENE fiber.[124] He also testified that there was no standard for mesh pore sizes and the mesh construction is measured or defined in courses and wales per inch, not pore size.

Experts for Plaintiffs proffer opinions that the TVT Classic design and material presented safety and effectiveness concerns and Ethicon should have considered alternative materials and designs.[125] For example, Dr. Klinge has stated:

> There are alternative design characteristics that would be safer in a woman's pelvic tissues as a treatment for incontinence than some of the design characteristics of the Prolene mesh in TVT. One such safer alternative design would be a mesh product with less material and larger distance between the mesh fibers (Ethicon's Ultrapro mesh has 3-5mm between the fibers and has a weight of 25 g/m2).
>
> Another safer design would be a polymer that elicits a more favorable inflammatory response. PVDF, as a synthetic, non-absorbable suture or mesh material has improved textile and biological properties over polypropylene. It is thermally stable and more abrasion resistant than other flouroplastics and induces a minimal cellular response, shows exceptional chemical stability and has excellent resistance to aging. PVDF sutures are routinely used in cardiovascular and orthopaedic surgery.[178]

And Dr. Elliot has discussed the characteristics of TVT and a "Prolene Mesh Improvement Project." Dr. Iakovlev has discussed an alternative material called PVDF.

The experts for Plaintiffs do not state whether any of the changes they proffer would be subject to FDA clearance of a new 510(k). The fact is that a new material or significant specifications changes to PROLENE described by Plaintiffs experts would have required a new 510(k).

I assessed the proffered changes as I did for 25 years as a premarket submission evaluator using FDA regulations and related guidance as a basis for my assessment. The FDA regulation for 510(k) submissions, 21 CFR Part 807, requires a new 510(k) be submitted for a marketed device as follows:[126]

> (3) The device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in

[122] ETH.MESH.00371539.
[123] ETH.MESH.08476244.
[124] Smith deposition, 2/3/14, Pages 721:19-24 and 727:22-25.
[125] Expert Reports 8/24/15, Prof. Dr. Med. Uwe Klinge, Bruce Rosenzweig, MD, Jerry G. Blaivas, MD, Dr. Daniel Elliot, Dr. Vladimir Iakovlev.
[126] 21 CFR §807.81(a)(3).

> design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:
> (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
> (ii) A major change or modification in the intended use of the device.

FDA guidance provides direction to the industry on the types of changes to an existing device cleared under a 510(k) that may be significant.[127] The guidance states the following:

> **Will the material of the affected part of the implant be likely to contact body tissues or fluids?** Changes in materials that contact body tissues or fluids may critically affect the device's safety or effectiveness, either because of potentially new interactions of the device material on the body or because of the body's environmental effects on the new material in the device. Manufacturers should submit a new 510(k) for a change in implant material where the material contacts tissue (including bone tissue) or body fluid.

In addition to the above recommendation by FDA the decision flowcharts in the guidance make it clear that a material change or formulation change, e.g., a weave change, to an implanted device leads to a new 510(k). In addition, Ethicon would be required to verify and validate the changes to the TVT Classic as required by the quality system regulation.

Some changes to the TVT Classic PROLENE material would not require a new 510(k). Each changed should be preceded by an assessment by Ethicon of the regulatory impact of the change. A change in color of the PROLENE strands, laser cutting or minor changes in the manufacturing process such as those listed in a deposition testimony exhibit[128] would not require a new 510(k) but would require consideration by Ethicon of the need for verifications and revalidation per the quality system regulation.

4. It is my opinion that there was no reason for FDA to recommend labeling changes to the TVT Classic. FDA requested changes to TVT Classic labeling before clearance in 1998.

FDA evaluates device labeling during the course of a 510(k) review to establish the intended use of the device and to identify other aspects that may need modification to ensure safe and effective use of the device. Once cleared, a device manufacturer may voluntarily modify labeling for several reasons, e.g., to improve it in some manner. Significant changes to labeling affecting safety and effectiveness require clearance by FDA.

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[127] Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.

[128] ETH.MESH.10633520.

From time to time FDA may post information on its web site to health care providers, the industry and the public on public health issues. Any imperative regulatory action directed towards manufacturers is not transmitted by means of these notices but rather through communications directly with the manufacturers.

FDA issued a public health notice in 2008. The salutation in the FDA Public Health Notification (PHN) issued October 20, 2008 on gynecological mesh is "Dear Healthcare Practitioner."[129] It advises physicians regarding training and technique and notably provides three imperatives to physicians to inform patients about risks with the devices. There is no recommendation directed to manufacturers.

The July 13, 2011 update to the PHN was only for transvaginal placement of surgical mesh for treatment of pelvic organ prolapse. A 2013 update to the FDA web site regarding mesh for the treatment of SUI includes information to health care providers and patients. There are no recommendations for manufacturers. Physicians are advised to inform their patients of the risk of using mesh for SUI. Likewise, patients are advised to "ask your surgeon about all SUI treatment options, including non-surgical options and surgical options that do and do not use mesh slings. It is important for you to understand why your surgeon may be recommending a particular treatment option to treat your SUI. Any surgery for SUI may put you at risk for complications, including additional surgery… Ask your surgeon the following questions before you decide to have SUI surgery…"[130]

FDA never recommended any labeling change to an Ethicon TVT device after clearance. FDA requested some labeling changes to TVT System labeling prior to the 1998 clearance including revision to the Indications for Use, Warnings, Adverse Effects, and Instructions for Use. Ethicon generally revised the labeling as requested.[131]

FDA cannot require a labeling change for a 510(k) cleared device but based on the public health notices and FDA's pronouncements there was no reason for FDA to even request such a change.

Ethicon proactively and voluntarily issued new IFUs and patient brochures as I describe in my opinions regarding the IFU and patient brochures. Ethicon also voluntarily revised its labeling in 2013.[132]

5. It is my opinion the FDA October 2008 Public Health Notice and subsequent updated FDA web information for health care workers and patients on treatment of SUI support Ethicon's position that the patient brochures were intended as only part of the interaction between the physician and patient regarding the potential treatment options for SUI and the warnings, precautions, and adverse effects for each option. This usage of patient brochures is consistent with industry practices and standards.

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[129] ETH.MESH.02252640-02252642.
[130] Information for Health Care Providers and Patients for SUI, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh.
[131] ETH.MESH.08476217-30.
[132] http://hostedvl106.quosavl.com/qb/doc/0nnlfm86hbpkf33bt7pl38flvg.

The testimony of Ethicon Medical Directors describe the role the patient brochures play in the informed consent process between the patient and her doctor. Dr. Charlotte Owens, Medical Director at Ethicon, testified regarding patient labeling:[133]

> "I think that one of the main things we have to do when we're speaking directly to patients, because they're – we're delivering products that come through physicians, is there's a lot of information to encourage them to have a conversation about this with their physician…you can convey general statements that initiate a conversation between the patient and their doctor to determine what's the best step."

Susan Lin, a regulatory manager at Ethicon, testified:[134]

> "So it is the doctor's responsibility to communicate the risk to the patient before implant[ing] this device."

Dr. Piet Hinoul, Medical Director at Ethicon testified:[135]

> "We make patient brochures available to facilitate the conversation between her and her doctor to come up with the right decision for her treatment."

The FDA October 2008 PHN described above in opinion 3 supports this belief. The PHNs clearly describe FDA's expectation that doctors provide the patient a written copy of the manufacturer's labeling and discuss options and risks with the devices and techniques. The 2013 FDA web information on SUI notes that physicians should provide the patient the patient brochure or labeling if available and make sure the patient understands the risks and complications.

In these pronouncements FDA does not say the labeling stands on its own as the sole source of information to the patient (or the doctor for that matter). Labeling is only one factor discussed by FDA in its advisory information to doctors and patients on treatment of SUI. It is clear the doctor, not the manufacturer, is a focus of FDA's notices on SUI due to the doctors key role as the learned intermediary who interacts with the patient.

6. It is my opinion there is no regulatory requirement concerning the content or format of prescription medical device patient brochures. The TVT brochures are not false or misleading. There is no requirement for "fair balance" in device labeling.

The medical device labeling regulation, 21 CFR §801, does not contain any requirement for patient labeling for a prescription medical device or requirements concerning the content of patient labeling. The prescription labeling requirements are devoted to the practitioner labeling. A manufacturer may voluntarily choose to provide patient

[133] Charlotte Owens deposition, June 20, 2013, Page 341:1-10.
[134] Susan Lin deposition, August 1, 2013, Page 1051:2-4.
[135] Piet Hinoul, MD. PhD, June 27, 1013, Page 407:3-6.

labeling and it is sometimes logical to do so, such as when the patient has a significant role in the use of the prescription device.[136] The patient labeling, if provided, are subject to the misbranding provisions of the act. Also, if patient labeling is provided then 21 CFR §801.109(d) can be interpreted to require attachment of information like an IFU to patient labeling.

FDA has published guidance concerning patient labeling but FDA guidance is voluntary for manufacturers. A statement in guidance is mandatory only if it is restating a law or regulation.[137] As the aforementioned guidance notes *"This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations."*

The term "fair balance" is a regulatory term applicable only to drug labeling.[138] From time to time persons may attempt to apply fair balance as a requirement to device labeling. As a concept fair balance in labeling may have merit on a case-by-case basis but there is no medical device statutory or regulatory requirement concerning fair balance in device labeling or advertising.[139]

Given the above regulatory criteria I have examined the TVT Classic patient brochures listed in Table 1.

TABLE 1 TVT Classic Patient Brochures

Brochure	*Bates*	*IFU information included*	*Information Included (examples)*
What you can do about it	*ETH.MESH.08003197-08003212*	*yes*	*What is SUI, options, TVT information, risks/benefits, discussions with doctor*
same title	*ETH.MESH.08003181-08003196*	*yes*	*as above*
Its Within Your Control	*ETH.MESH.08003173-08003180*	*yes*	*as above*
Breaking the ice about SUI	*No Bates*	*yes*	*as above*
The Choice to End SUI	*ETH.MESH.08003247-08003262*	*yes*	*as above*
same title	*ETH.MESH.08003263-08003278*	*yes*	*as above*
same titles	*ETH.MESH.08003215-08003230*	*yes*	*as above*

[136] A PMA approval may require patient labeling as a condition of approval, or a regulation may require patient labeling for a specific device. Neither of these apply to TVT.
[137] Guidance on Medical Device Patient Labeling, http://www.fda.gov/MedicalDevices/DeviceRegulationand Guidance/GuidanceDocuments/ucm070782.htm.
[138] 21 CFR Part 202, Prescription Drug Advertising
[139] There are advertising provisions for restricted devices in 502(q) and (r) of the act but TVT is not a restricted device.

same title	*ETH.MESH.08003231-08003246*	*yes*	*as above*
stop coping, start living	*ETH.MESH.08003279-08003294*	*yes*	*as above*
same title	*ETH.MESH.08003303-08003318*	*yes*	*as above*
same title	*ETH.MESH-08003295-08003302*	*yes*	*as above*

In general, in all the patient brochures the patient is advised to talk to her doctor about her condition, the treatment options, and the risks and benefits. This is consistent with the FDA public notice instructions regarding communication between doctors and patients concerning treatment of SUI as detailed in this report.

In my opinion, the risk section accurately states the fact that all surgical procedures present risks. Risks are listed in all brochures and the patient is referred to the IFU information for a complete description of risks, and informed to talk with her doctor about the risks. Again, statements in the brochures on communication between doctor and patient are consistent with the FDA PHN instructions to doctors and patients concerning treatment of SUI.

The potential or claimed benefits of TVT are discussed in the brochures. The dates of the brochures were produced at different times so the information contained in the brochures cannot be expected to remain static. In my opinion the claims of minimally invasive are supported, considering the comparison is the alternative open abdominal procedures for treatment of SUI. The claim of less operative time is supported compared to open procedure operative times. The long-term safety and effectiveness claim is supported, given that TVT devices had been marketed for years (TVT Classic cleared in 1998).

7. It is my opinion that the FDA recall and Warning Letter databases do not document common or unusual TVT device manufacturing problems.

On January 29, 2016, I reviewed a record of recalls and FDA inspections for the TVT devices. From a previous examination of the database I identified one recall in 2000 for the TVT Classic due to needle pull off from the tape, which Ethicon immediately addressed.[140] There were no additional recalls for TVT in the current public FDA database.

FDA may issue Warning Letters based upon evidence collected during an inspection demonstrating violations of the act. My review of the FDA Warning Letter database identified no Warning Letters to Ethicon related to Ethicon TVT devices.[141]

I evaluated the inspections by FDA of an Ethicon facility in Somerville, NJ, where TVT manufacturing activities are conducted. An FDA inspection in 2005 resulting in one observation by FDA related to

[140] ETH.MESH.00108420-00108423.
[141] FDA Warning Letter database, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters. Examined on January 29, 2016.

MDR reporting and not manufacturing. Ethicon responded thoroughly to this observation.[142] The establishment inspection report for the 2005 inspection notes two prior inspections in 2004, one unrelated to TVT and the other resulting in no observations. FDA identified no defects in manufacturing or in the TVT devices was identified.

My review of TVT Issue Reports (See opinion 11) include product related complaints that meet the FDA definition of malfunctions such as tip breakage, split sheaths, open packaging, needle/trocar breakage, and the tape coming off the needle. According to Ethicon complaint procedures (See opinion 8) Ethicon investigated these events and trended the complaints. Complaint trends may identify manufacturing nonconformities that require corrective and preventive action. I did not identify significant records of CAPAs for Gynecare TVT related to manufacturing defects.

In sum, there is no basis from FDA inspection and recall data to conclude that the TVT device had common or unusual manufacturing defects.

8. In regard to the design and manufacturing of the Gynecare TVT device, Ethicon was proactive in striving to ensure that its complaint and medical device reporting procedures, training of staff on those procedures, implementation, and documentation were substantially compliant with regulations. FDA regulations permit manufacturers to determine whether or not a complaint is a reportable event based on causation. Ethicon's procedures were consistent with industry standards and practices.

Complaint collection and investigation is an important quality management process according to the FDA quality system regulation. Complaints may describe patient-related events that may be reportable to FDA according to the medical device reporting regulation. FDA regulations are not completely prescriptive in how a manufacturer must comply with complaint and reporting requirements. Mush of the details in how to construct procedures and policies and work instructions are left to the manufacturer who in turn relies on industry standards and practices in meeting the requirements.

In evaluating whether Ethicon met FDA requirements and used industry standards and practices in regard to complaint handling and reporting I examined their procedures and how they implemented those procedures.

Franchise Policy for Product Complaint Management, PL0000087 undated[143], states, “it outlines the required elements for all complaints relating to ETHICON franchise products to ensure compliance to J&J policy, regulatory requirements, and voluntary standards.” It is a high level document and describes the general regulatory elements for complaint and MDR processes. It does not address CAPA except in terms of

[142] ETH.MESH.00319683, 04095019-25.
[143] ETH.MESH.03743182-03743193.

escalation to CAPA. It is the first revision of the policy[144] put in place in 2010.

A version of the Franchise Complaint Procedure, PR-0000118, version 18,[145] put in effect in 2011 provides details on elements of the complaint process described in the above policy. Some of the key elements include certain definitions such as adverse event and incident, minimum information required in a complaint file, complaint investigation, design history review, medical review, serious injuries, deaths and/or incidents. In regard to medical review the procedure states for 5.2.8."(Medical) Review may be requested to help in determination of device relationship to reported event, to determination of severity of an event for purposes of adverse event reporting."[146] Section 5.2.11.4 states "Medical Assessment: For the reported event, the WCQ Medical Director will write a medical assessment based on the reported complaint information and include one of the following conclusions in the investigation comments (refer to Appendix V for definitions):

- The Device Caused Event
- The Device Contributed to Event
- The Device Potentially Contributed to Event
- The Device Not Likely Related to Event
- The Device is Not Related to Event
- Not Enough Information to Draw a Conclusion

If the Medical Assessment concludes that the device Caused, Contributed to or Potentially Contributed to the Event, then the medical assessment should also include commentary on whether or not the resultant harm is an anticipated outcome of the device or that the outcome is noted in the labeling."

The Franchise Procedure for Summary and Individual Medical Device Reporting, PR551-06, revision 30,[147] provides detailed procedures for MDR decision-making. It includes summary decision trees including the elements of death and serious injury and malfunction related aspects, and whether the event may be related to the device. It includes consideration whether there is information or medical rationale that states the device did not cause or contribute to a death. It includes aspects not in the MDR regulation but company specified steps such as treatment of litigation files, sutures, and packaging.

The April 7, 2013 deposition of Mark C. Yale, manager of wordwide customer quality for Ethicon for a period of time addresses Ethicon's complaint process. Mr. Yale testified on the content of the Ethicon Franchise Instructions for Summary and Individual Medical Device Reporting, PR551-006 Rev.31, 7 Sept 2012.[148]

The MDR procedures meet the requirements of 21 CFR Par 803, the MDR regulation in that the multi step reporting decision process includes all the key elements in the regulation such as death or serious injury, intervention, and malfunction determinations. The process includes some Ethicon-specific steps such as steps 4a-4d of revision 31. These

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[144] Lamont deposition, 4/5/12, page 485:4-7.
[145] ETH.MESH.03743365-03743387.
[146] Lamont testifies that this was in place since 2006, Lamont deposition, 4/5/12, page 492:8.
[147] ETH.MESH.03589458-03589480.
[148] ETH.MESH.07277675-07277696

variations are permitted by the MDR regulation.

An internal audit of quality system aspects including complaint, MDR and CAPA procedures in 2002, according to Mt. Yale[149] includes observations related to documentation, the need for some clarity in procedures, a few procedural lapses. Internal audits are a requirement of the quality system regulation, 21 CFR §820.22 to help ensure the quality system is in compliance and for continuous improvement purposes. FDA does not inspect these audit reports or any CAPAs initiated due to these audits in order to encourage self improvement by a company.

Deposition records indicate that Ethicon is committed to proper training of staff and reporting compliance as evidenced by several staff emails.[150]

The MDR regulation requires manufacturers to assess complaints and to report events that reasonably suggests that a device they market for "may have caused or contributed to a death or serious injury; or has malfunctioned and this device or a similar device that you market would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur."[151]

Caused or contributed means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of:[152]
(1) Failure;
(2) Malfunction;
(3) Improper or inadequate design;
(4) Manufacture;
(5) Labeling; or
(6) User error.

Manufacturers are required to have staff with the education, background, training and experience necessary to adequately perform their required duties.[153] Ethicon complaint/MDR procedure included the option to obtain Medical Director input on a complaint to determine reportability.

In the deposition testimony of Mark Yale three events are discussed that were not reported due to the conclusions of Charlotte Owens, the Medical Director at that time.[154] Not being a clinician I will not render a medical opinion on her conclusions but note that her input and conclusions are permissible according to the MDR regulation.

While the quality system regulation provides the framework for a quality management system it is industry standards and practices that enable a manufacturer to fully implement such a system.

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[149] Yale deposition, 2013, page 151:11
[150] ETH.MESH.01949198-01949200, ETH.MESH.03531443-03531448, ETH.MESH.01814250-01814252, ETH.MESH.00318881-00318889, ETH.MESH.00874613-00874615, ETH.MESH.06496130-06946134
[151] 21 CFR §803.50(a)(1)(2).
[152] 21 CFR §803.3.
[153] 21 CFR §820.25(a).
[154] ETH.MESH.03575123, ETH.MESH.03575101, ETH.MESH.03575054.

10. In regard to the design, manufacturing, testing and marketing of the Gynecare TVT Classic Ethicon substantially complied with all FDA premarket and related quality system requirements prior to and during marketing for the TVT Classic including, for example, 510(k) and design control requirements. Ethicon's launch and continued clinical use of the TVT Classic was supported by clinical assessments of benefit vs risk.

In general, FDA regulations require a new device to be cleared or approved, unless otherwise exempt from such requirements, before it can be marketed.[155] In this report I document the 510(k) clearances for the listed Ethicon TVT devices. FDA concluded that the devices were all substantially equivalent to predicate Class II devices.

FDA regulations permit a manufacturer to make changes to a cleared device without submitting a 510(k) if the manufacturer concludes that the change could not significantly change or modify the device in design, material, chemical composition, energy source or manufacturing process.[156] In my experience it is common that manufacturers make changes to their devices or manufacturing processes and document their decisions regarding these types of changes during the course of marketing their devices.

I evaluated the Gynecare TVT Clinical Expert/Evaluation Report and 510(k) to identify the validations performed prior to marketing this TVT device, and the benefit/risk assessments as follows:

Section 5 of K974098[157] documents clinical data from Ulmstem and a multi-center Scandinavian study, both using a Prolene sling,[158] and additional clinical literature. The June 15, 2000, Clinical Expert Report by Richard A. Isenberg, M.D. for TVT lists the primary and secondary benefits of TVT and side effects.[159] His risk-benefit analysis concludes that the benefits of TVT usage outweigh the risks. Supplemental analyses provided by Petra Kohler, Dan Smith and Martin Weisberg support modifications to the original device.

A Clinical Evaluation Report,[160] August 2, 2010, by Dr. David Robinson includes assessment of data and information on the TVT Classic to that point in time, including literature, complaint/adverse effect data, labeling, and risk/benefit analysis. Dr. Robinson concludes there were no additional harms/hazards compared to labeling and the internal complaint database.

Piet Hinoul testified comparing a TVT patient brochure and claims of low-risk, minimally invasive and rare complications compared to the Burch procedure:[161]

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[155] 21 CFR §807.81 and 21 CFR §814.1.
[156] 21 CFR §807.81(a)(3).
[157] ETH.MESH.00371496-00371514.
[158] Ulmsten describes Prolene tape dimension as 40cm long and 10mm wide.
[159] ETH.MESH.07226579-590.
[160] ETH.MESH.00831361-00831400.
[161] Hinoul deposition, 6/27/13, page 411:6-14.

"And certainly if you hold the data on this device to what we used to do in the past, being the Burch colposuspension, where patients would have to go in the hospital for a week, undergo a big cut in the abdomen, a laparotomy, a very difficult procedure to learn, very difficult procedure to recover from. So I would absolutely agree with what is stated in that brochure."

Dr. David Robinson testified regarding the Burch procedure compared to TVT:[162]

"Eventually the TVT became the gold standard."

The design control regulation requires procedures for design and development planning, design inputs, design outputs, design review, design verification and validation and design transfer.[163] The design history file "contains or references the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of (the quality system)."[164] The design control file for the TVT-O device,[165] inasmuch as it is evidence of Ethicon's execution of design control requirements for all its TVT devices, is complete and comprehensive as evidenced by sections and thorough records relating to all the above requirements.

Mr. Smith testifies:[166]

Q: "Is there also a design history file for TVT Blue?" (question repeated for TVT-AA, TVT-O, EXACT, SECUR, TVT D)

A: "Yes"

He also testifies:[167]

Q: "So for the TVT Classic is there a design history file? Does Ethicon have a design history file for the TVT Classic?"

A: "To the best of my knowledge, there's documentation for every one of these products."

I have examined documents that would be included in a design history file for TVT Classic.[168] Records comprising a Design History file need not be maintained in one location.[169] The Design Control requirements of the Quality System Regulation became effective until June 1, 1997 and FDA provided a grace period for manufacturers to comply with this portion of the Quality System Regulation until June 1, 1998. For those devices already on the market FDA did not intend for Design Controls to

[162] Robinson deposition, 7/24/13, page 45:10-11.
[163] 21 CFR §§820.30(b)-(h).
[164] 21 CFR §820.30(j).
[165] Smith deposition, 5/15/13, Exhibits T217, T223-228.
[166] Smith deposition, 5/15/13, pages 108:6-109:11
[167] Id. page 95:21-25.
[168] ETH.MESH.01317508-613.
[169] 21 CFR §820.30(j).

be retroactive.[170] Since TVT Classic was cleared on January 28, 1998 Ethicon was not required to have a Design History file for this device at that time.

11. In regard to the design, manufacturing, labeling and marketing of the Gynecare TVT device, the Issue Reports and the associated Medwatch reports are indicative of Ethicon's substantial compliance with complaint and MDR regulatory requirements as well as consistency with industry standards and practices.

I examined the following Issue and Medwatch (MDR) Reports for Ethicon Gynecare TVT:

Device	Type Report	Open Dates	Pages	Starting Bates
TVT Retropubic	Issue	1/1/99-2/1/12	11651	02620354
TVT Retropubic	Medwatch		3681	03578058
TVT Retropubic	MDRs	2012-2015	FDA web site	N/A

A single Ethicon internal Issue Report is approximately 8 pages while a single Medwatch Report to FDA is 2 or 3 pages for the FDA Medwatch Form 3500A.

I have the following observations from my review of these reports:

1. Ethicon Issue Reports document complaints, their investigation by Ethicon, and Ethicon's decisions determining whether a complaint is reportable to FDA.

2. The Issue Reports document complaints concerning procedure and post procedure related events. The procedure complaints include "out of box" problems like packaging problems, device malfunctions during the procedure like tip or needle breakage and split sheaths, and procedural mishaps like cutting of the bladder or a vein. The post procedure events include, for example, hematomas, exposure, exposure, pain, bleeding, retention, erosion, voiding issues, infection, fistulas, nerve issues.

3. The MDRs, based on the Issue Report events, include, for example, events describing procedural errors, malfunctions, exposures, erosion, nerve issues, pain, retention and other voiding problems.

4. There are rare reports of shrinkage, tissue reaction and scarring.

5. Complaints originate from a variety of sources such as health care facilities, doctors, patients, journals, and salespersons.

6. Events not resulting in MDRs generally include those where there was no patient effect reported, the injury resolved without intervention

[170] Preamble to QSR, comment 64, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/ucm230127.htm.

such as some, but not all, bladder cuts or post operative pain, or where the event was determined to be unrelated to the device.

I reviewed a Complaint Vigilance Audit Report dated February 2002[171] and an Independent MD&D Sector Audit of Ethicon MDR process in 2012.[172] These internal audits are required by regulation but are not inspected by FDA. The audits are part of the continuous improvement process in a company. The purpose of the audits is to make observations of a system which the company can then improve. I agree with Catherine V. Beath who testified regarding these audits:[173]

"I'm confident we had a plan to address them (the identified issues). You're always trying to improve."

"But this (the 2012) audit basically said the reporting decisions are consistent with regulations and FDA guidance. The information and rationale to support a decision is sometimes inadequate."

She also testified:[174]

"Based on a number of inspections that they (FDA) have done at the Somerville facility, almost always of the complaint MDR system, I think they're pretty confident that we follow the regulations and that when we find we have gaps, we correct them. As a matter of fact, they've told us that, that they have a lot of confidence in Ethicon to correct problems."

In sum, based on my observations, the internal audit reports, lack of FDA enforcement action regarding Ethicon's complaint and MDR procedures, and considering the regulatory requirements for complaint handling and medical device reporting I find them supporting Ethicon's substantial compliance with those requirements.

12. In regard to the design and testing of the Gynecare TVT device, the clinical evidence supporting the safety and effectiveness of Ethicon TVT devices were of a sample size and duration consistent with clinical evidence in other 510(k) devices and even with several PMA approved devices.

During the course of my career at FDA and now as a consultant I have created clinical protocols and evaluated clinical protocols and data used to support the marketing of medical devices.

In the 510(k) for the Gynecare TVT, Ethicon submitted clinical evidence supporting the safety and effectiveness of transvaginal tape for the treatment of SUI. These data included:[175]

> Medscand TVT device: U. Ulmsten, et al., An Ambulatory Surgical Procedure Under Local Anesthesia for Treatment of Female Urinary Incontinence. Non-randomized, prospective. 75 subjects, 2 year follow up.

[171] ETH.MESH.02249640-642.
[172] ETH.MESH.07724068-080.
[173] Beath deposition, 7/12/13, pages, 561:23-24 and 569:4-7.
[174] Id. pages 576:23-577:5.
[175] ETH.MESH.00371551.

Medscand TVT device: M. Erikson, Scandinavian Multicenter Study of the Tension Free Vaginal Tape Procedure. Non-randomized, prospective, multi-center. May 1997, 131 subjects, 1 year follow up.

Wang, A.C. and Lo, T.S., Tension-Free Vaginal Tape for Urinary Stress Incontinence. July 1997, 83 subjects, 3-12 month follow up.

Blaivas, J.G. and Romanzi, L., Pubovaginal Fascial Sling for Type 1 & 2 Stress Incontinence. 1996, 28 subjects, 1-6 year follow up.

Leach G.E. et al Female Stress Urinary Incontinence Clinical Guidelines. Review of 284 clinical articles comparing techniques. Sling procedure patient number is 473 with follow up of greater than 48 months.

The Institute of Medicine's report Medical Devices and the Public Health: The FDA 510(k) Clearance Process at 35 Years assesses the 510(k) process and provides recommendations to FDA.[176] The report on page 107 refers to a GAO study which identified that only 15% of 510(k)s submitted during FY2005-2007 include clinical data. The IOM and GAO did not evaluate or make a recommendation regarding the type or quality of clinical data used to support 510(k) devices.

It is evident from the IOM report that clinical data is not often required in a 510(k). One reason is that the new device can rely on the clinical experience with similar devices. Clinical data is needed when there is a clinical issue that cannot be answered by prior clinical evidence, engineering data or simulations. Clinical data is needed for a premarket approval application by law but also due to the fact that there are no prior devices similar enough to enable the use of prior clinical experience.

In my experience, when a 510(k) includes clinical data, the number of subjects enrolled in the supporting clinical studies and the post-treatment follow up is often similar to the clinical data supporting the Gynecare TVT that I reference above.

The 510(k) for the Gynecare TVT was cleared in 1998. FDA completed 40 PMAs in 1998 and 36 in 1999.[177] I examined original premarket approval summaries on FDA's web site[178] for 1998/1999, to identify the subjects enrolled in the clinical studies for each PMA and the duration of subject follow up. My simple hypothesis was that the Gynecare TVT study enrollment and follow up was similar to contemporaneously approved PMA devices.

In this cohort of PMAs there were several submissions for implants, some of which had clinical study enrollment in the range of 31 to 200

[176] IOM Report, http://www.iom.edu/Reports/2011/Medical-Devices-and-the-Publics-Health-The-FDA-510k-Clearance-Process-at-35-Years.aspx.
[177] ODE Annual Report, http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm199014.pdf.
[178] FDA PMA database, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm.

plus subjects and post-treatment follow up varying between a few weeks to 6,12 or 24 months.[179] The PMA clinical study for a bulking agent used for the treatment of SUI had 178 subjects enrolled in the treatment group, and 177 control subjects with a 12-month follow up.[180]

The enrollment and follow up clinical study parameters for the above PMA approved devices are not extraordinarily different than the same parameters in the clinical evidence in the 510(k) for the TVT System.

In sum, the clinical evidence submitted in the TVT 510(k) was more than 85% of 510(k)s submitted in 2005-2007 and the data was commensurate with PMA clinical data at that time.

13. In regard to the design and testing of the Gynecare TVT device, the FDA's evaluation of substantial equivalence in a 510(k) includes an analysis of the safety and effectiveness of the device.

In August 2010, an FDA 510(k) Working Group carefully assessed the 510(k) program and provided recommendations to senior FDA management.[181] The report states the following in regard to safety and effectiveness determinations in 510(k)s (emphasis added):

> "With the exception of certain lower risk devices that are exempt from premarket review, CDRH reviews the safety and effectiveness of medical devices for their intended use prior to marketing. Under the premarket approval (PMA) process, each manufacturer must independently demonstrate reasonable assurance of the safety and effectiveness of its device for its intended use. Under the premarket notification (510(k)) process, CDRH will clear a new device if it finds, through review of a 510(k) submission, that the device is substantially equivalent to a predicate. Generally, predicate devices, as largely class II devices, are those for which there is a reasonable assurance of safety and effectiveness with general and applicable special controls."
>
> "The 510(k) program, as it currently exists, is intended to support FDA's public health mission by meeting two important goals: making available to consumers devices that are safe and effective, and fostering innovation in the medical device industry."
>
> "When a predicate has a well established risk/benefit profile and is generally well regarded by the healthcare community, a premarket comparison of a new device to that predicate, with sufficient information, can provide reasonable assurance that the device, subject to general

[179] Examples: P990033, P990002, P990004, P970015, P980052
[180] P980053.
[181] CDRH Internal Preliminary Evaluations – Volume 1, 510(k) Working Group, Preliminary Report and Recommendations, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsand Tobacco/CDRH/CDRHReports/UCM220784.pdf.

> and applicable special controls, is safe and effective for its intended use."

The determination of safety and effectiveness in both a PMA and a 510(k) is based on the statutory and regulatory standard of valid scientific evidence, as stated in regulations as follows (emphasis added):[182]

> "(1) Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. After considering the nature of the device and the rules in this section, the Commissioner will determine whether the evidence submitted or otherwise available to the Commissioner is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.
>
> (2) Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use."

The Act has been amended several times.[183] One such change was the Medical Device User Fee Act of 2002 (MUFMA).[184] According to FDA, MDUFMA was enacted "in order to provide the Food and Drug Administration (FDA) with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical device manufacturers can bring their safe and effective devices to the American people at an earlier time…"[185]

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[182] 21 CFR §860.7(c)(1).
[183] Amendments to the Federal Food, Drug and Cosmetic Act, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/default.htm.
[184] PL 107-250 (Oct. 26, 2002).
[185] MDUFA, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109149.htm.

A 2014 guidance issued by FDA on the determination of substantial equivalence notes the following (emphasis added): "Because devices are classified according to the level of regulatory control necessary to provide a reasonable assurance of safety and effectiveness, classification of a new device through the 510(k) process requires FDA to determine the issues of safety and effectiveness presented by the new device, and the regulatory controls necessary to address those issues."[186]

The guidance goes on to state "The 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate device) differs from the PMA review standard (reasonable assurance of safety and effectiveness) in that the 510(k) review standard is comparative whereas the PMA standard relies on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."

14. It is my opinion that the labeling for the TVT Classic is substantially compliant with regulatory requirements and industry standards and practices.

I examined the following TVT Classic Instructions for Use (IFUs):

TVT Classic IFU	Bates	IFU contents
Launch version	ETH.MESH.05225354-85	Indications, contraindications, warnings, precautions, adverse reactions, actions, how supplied, storage, instructions for use, Rx statement
2nd version	ETH.MESH.02340306-69	as above
Third version	ETH.MESH.02340471-503	as above
Fourth version	ETH.MESH.05222673-704	as above
Fifth version	ETH.MESH.02340504-567	as above
Sixth version	ETH.MESH.03427878-945	as above
current version	Ethicon web site	as above

The adverse reactions section in all the above IFUs for the TVT Classic, except for the current version, included the following:

[186] Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], http://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf.

ADVERSE REACTIONS

- Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair.
- Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.
- As with all foreign bodies, PROLENE mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE mesh is designed to minimize the risk of contamination.
- Over correction i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.

The current version of the TVT IFU, viewed on 1/19/16, expands the adverse reactions section to include the following:

ADVERSE REACTIONS

- Punctures or lacerations of vessels, nerves, structures or organs, including the bladder, urethra or bowel, may occur and may require surgical repair.
- Transitory local irritation at the wound site may occur.
- As with any implant, a foreign body response may occur. This response could result in extrusion, erosion, exposure, fistula formation and/or inflammation.
- Mesh extrusion, exposure, or erosion into the vagina or other structures or organs.
- As with all surgical procedures, there is a risk of infection. As with all foreign bodies, PROLENE Mesh may potentiate an existing infection.
- Over correction, i.e., too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction.
- Acute and/or chronic pain
- Voiding dysfunction
- Pain with intercourse which in some patients may not resolve.
- Neuromuscular problems, including acute and/or chronic pain in the groin, thigh, leg, pelvic and/or abdominal area may occur.
- Recurrence of incontinence
- Bleeding including hemorrhage, or hematoma.
- One or more revision surgeries may be necessary to treat these adverse reactions.
- PROLENE Mesh is a permanent implant that integrates into the tissue. In cases in which the PROLENE Mesh needs to be removed in part or whole, significant dissection may be required.

OTHER ADVERSE REACTIONS

- Seroma
- Urge incontinence
- Urinary frequency
- Urinary retention
- Adhesion formation
- Atypical vaginal discharge
- Exposed mesh may cause pain or discomfort to the patient's partner during intercourse.
- Death

I also examined the warnings and precautions sections for all the IFUs. All the IFUs fundamentally meet the regulatory requirements for prescription labeling in that all the IFUs have the required prescription labeling elements.[187] The adverse reactions section is structured in a manner consistent with industry standards for medical device labeling. Adverse reactions sections for devices do not typically list the frequency of reactions nor are they necessarily ordered in severity.

Medical device labeling, except for PMA approved devices, do not typically include a section discussing the clinical evidence related to the medical device. This makes perfect sense since new clinical evidence is frequently being published (see 2013 CER by Piet Hinoul). The TVT IFUs appropriately do not contain such a section.

IFU information evolves over time for many reasons, in this case the current thinking of FDA and its expert panel regarding SUI. I know from my experience at FDA as the chief device labeling compliance officer that common knowledge and training of doctors regarding diseases and treatments weighs heavily in FDA's consideration of what is appropriate to place in labeling. IFUs are not textbooks of medical practice. For these reasons IFUs could never list all the adverse events that potentially could be encountered in the use of a medical device.

I defer to clinical expertise, including that of Ethicon's medical directors, regarding the scope, content and interpretation of the warnings, precautions and adverse reactions in the TVT Classic IFUs.

Catherine V. Beath, VP QA/RA at Ethicon, testified regarding the role of the medical directors in deciding the content of labeling:[188]

> …all of the medical directors that I knew that were in the business actually implanted these devices, they had done procedures, so they were the best experts to tell us when it would be appropriate for other physicians like them where the information would be useful.

OPINION 16. It is my opinion that the adverse press and litigious environment after the 2011 FDA Safety Notice resulted in an atypical surge of MDR reports.

I describe in this report the FDA notices and the September 2011 meeting of the FDA Obstetrics and Gynecology Advisory Committee. The Committee discussed the benefits and risks of pelvic mesh and transvaginal tape. On July 13, 2011, FDA posted a Safety Communication of Pelvic Mesh for POP.

In my experience, and as I note below from FDA statements and the literature, those implanted with a TVT device (or who think they may have a TVT device) may become aware of FDA activity and publicity concerning TVT devices from various sources including, for example,

[187] 21 CFR §801.109.
[188] Catherine V. Beath deposition, July 11, 2013, Page 198:19-24

their doctor or from the media, such as lawyer advertisements.[189] Patients may become concerned about the effect, if any, that the device has on their future welfare based on the media reports. Researchers note "Clinicians should be aware of the impact of these advertisements on patient opinion and counsel patients accordingly with unbiased and scientifically accurate information."[190]

During the period from 2011 onward there was considerable public information and media attention on pelvic mesh, including information FDA posted on its web site.[191] Koski's 2014 publication notes the following regarding transvaginal mesh:[192]

> Clinicians have encountered patients with heightened concern regarding the mesh. For example, it is currently not uncommon for patients several years out from a TVM procedure with no complications or symptoms to present questioning whether their mesh should be removed. Although there is a high value in patient awareness of these issues as well as in discussion between patients and physicians, information disseminated in a nonmedical environment and outside of the proper context could result in unnecessary patient anxiety or fear.

FDA believes that effective medical risk communication on matters of public health interest like pelvic mesh is important to inform doctors and assist them with patient care, and to also inform patients and to provide current recommendations and answer questions. At the patient follow up visits the doctor and the patient have the opportunity to discuss this information and the future course of clinical care. The doctor's ability to influence patients' decisions may be hampered when patients become aware of information on a device (that may be biased due to certain pecuniary interests) they may have been treated with before their doctor can inform them of accurate information and discuss it with them.

In its Strategic Plan for Risk Communication[193] FDA states "…the ultimate decision about whether to act on warning information (such as a recall notice) is made by an individual, taking into account the information received, his or her own knowledge, values, and, sometimes, consultation with a medical professional. But each person needs to receive and understand the information necessary to help inform choices.

FDA provides an illustration of challenges with implanted devices as follows:

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[189] Michelle Elaine Koski et al, Patient Perception of Transvaginal Mesh and the Media, Urology 84:575-582.
[190] Id.
[191] Id. and 8/2/15 web search reveals 13,300 results using keywords "pelvic mesh lawsuits."
[192] Id.
[193] Strategic Plan for Risk Communication, Urology, 84(3), 2014:575-582. http://www.fda.gov/aboutfda/reportsmanualsforms/reports/ucm183673.htm.

Example 1: Implanted Devices

The Facts: Many American families have a member with an implanted device helping to keep a regular heartbeat. After years of experience with the device implanted in many people, the manufacturer learns that a small device piece may fail in an extremely small number of people. The manufacturer and FDA decide that devices that have not yet been implanted should be recalled. In most cases, the risks of removing the device outweigh the risks of leaving the device in, given the benefits of the device for the patient. How does communication ensure a successful recall of the remaining devices without causing undue concern for those with the device already implanted?

The Challenge: Some worried patients may make unnecessary office visits, and even potentially harmful decisions about removing a device that is providing a significant benefit—a benefit that outweighs the risk of device failure.

Effective risk communication: Effective risk communication achieves both of the desired ends—an effective recall and an informed patient—in a way that avoids patients making potentially costly and dangerous decisions. This generally means that a complex set of risk and benefit information must be communicated in a way that consumers will attend to, understand, and be able to apply to their individual situations.

In a paper on health care policy and regulatory[194] the authors state "Field actions taken by a manufacturer are often very expensive and come with an attendant amount of attention, publicity, and legal action. While this attention provides significant opportunities to inform physicians and patients, it often leads to fear and—sometimes—inappropriate actions." Physicians and patients may decide to remove devices that are functioning well.

FDA recognized the effect of litigation and other actions on reporting of medical device reports. In information provided to the Orthopedics Advisory Panel in 2012 FDA stated:[195]

> "Recalls, negative media attention, litigation, and increased/decreased usage of a medical device may substantially increase or decrease the number of MDRs received by the FDA. The recall for the DePuy ASR (August 23, 2010) contributed to the sharp increase in MoM THR MDRs received in 2010 and 2011. For example, of the 12,137 MoM THR reports received in 2011, DePuy ASR accounted for 9,006 of these reports (74.2%)."

In my experience in dealing with many instances of increased media concerning a device I can confirm the above statement that various media result in patient and physician responses that will affect clinical results and may result in increased medical device reports to FDA. In every meeting I had with manufacturers of implants associated with media attention the risk of unnecessary explants existed and immediate, effective risk communication necessary.

The following figure displays the atypical surge in TVT MDRs after the increase in media attention, e.g., lawyer ads, in 2011 concerning

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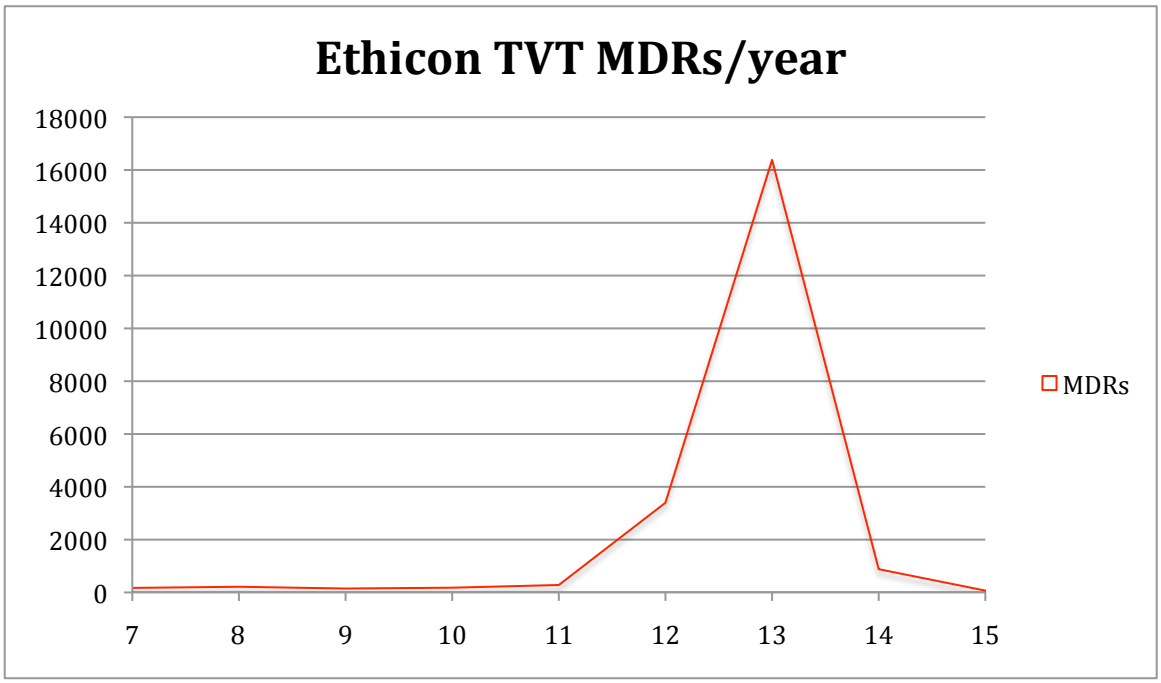
[194] Sharma, A, et. al., Health care policy and regulatory implications on medical device innovations: a cardiac rhythm medical device industry perspective, J Interv Card Electrophysiol. 2013 March; 36(2):107-117.

[195] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM309406.pdf.

pelvic mesh. The trend of MDR submissions before 2011 was a slowly increasing straight line with fewer than 300 reports during 2011. I would have expected during the normal course of reporting that the established trend would continue. However, in 2012-2014, after the increase in media attention, the MDR reports increased 40 fold.[196] The vast majority of MDR reports during 2012-2014 are from attorneys while before 2011 the reports are from the manufacturer or from user facilities. In 2015 the MDRs submitted have returned to pre-2012 levels.



As I noted, companies and FDA attempt to reduce unnecessary explants through effective risk communication. The FDA has posted on its web site the following information regarding pelvic mesh implants to decrease unnecessary surgeries:[197]

- Continue with your annual and other routine check-ups and follow-up care. There is no need to take additional action if you are satisfied with your surgery and are not having complications or symptoms.

In sum, a surge in MDRs occurred from 2011-2014 when media attention, e.g., legal advertisements, increased. This surge skews the probable true clinical risk profiles for the devices. As I note, the unbiased trend is reflected in the pre-2012 MDR submission statistics.

VIII. Comments Regarding October 14, 2013 Expert Witness Report by Peggy Pence, PhD., RAC, FRAPS

[196] MDR analysis conducted 9/30/15. MDRs include all Ethicon TVT devices.

[197] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345205.htm.

I have the following comments regarding Dr. Pence's October 14, 2013 report on TVT Classic. They do not necessarily comprise all the comments I may have on her report. To the extent Plaintiffs designate another ostensible regulatory expert, as opposed to Peggy Pence, who offers similar opinions, my responses will be similar:

1. Dr. Pence states on page 8 "FDA does not design and conduct either nonclinical or clinical studies to support device safety and effectiveness." As stated, this is not correct. Within the FDA Center for Devices and Radiological Health is the Office of Science and Engineering Laboratories (OSEL). The purpose of this office is described as follows:[198]

The Office of Science and Engineering Laboratories (OSEL), one of seven Offices within CDRH, contributes to the Center's mission by providing laboratory data and consults. OSEL serves as the laboratory science nucleus for the Center. Specifically, OSEL supports the scientific basis for the Agency's regulatory decision- making by developing independent laboratory information for regulatory and other public health activities of CDRH. In addition to providing consultation to the Center's regulatory experts, OSEL researchers are involved in mission-oriented science activities including test methods development, risk assessments, forensic investigations, product evaluations, and technology assessment.

From a science breadth standpoint, OSEL conducts laboratory and field research in the areas of physical, life, and engineering sciences as related to the effects of medical devices on human health. CDRH relies upon this work to support its efforts ensuring public safety in areas as varied as medical imaging, medical device software, breast implants, or drug eluting stents.

2. On the same page Dr. Pence states "FDA maintains a passive postmarketing surveillance system." This is partially the case. The Medwatch program is passive in that FDA relies on persons to submit required or voluntary reports of device-related deaths, certain injuries or malfunctions. However, FDA uses proactive means to assess device performance and safety including, for example, postmarket surveillance studies (522 studies), analysis of literature, and analysis of registries.

3. Dr. Pence refers on page 8 to Institute of Medicine and the Government Accountability Office reviews of FDA and states that these (unreferenced) reports have recognized "FDA lacks the capacity to provide adequate oversight." Dr. Pence does not provide FDA management's response to these reports. In my experience in senior management positions in FDA I am unaware of significant resource deficiencies in the areas of premarket evaluation and compliance. In fact, user fees helped provide FDA with the resources to fulfill their core responsibilities.

4. I have reservation regarding Dr. Pence's opinion on page 9 that "reasonably prudent medical device manufacturers are always expected to err on the side of caution, i.e., regulatory compliance, when faced with any uncertainty or ambiguity in the regulations." She does not describe whose expectations to which she refers. It goes without saying that manufacturers must always strive to be compliant with regulations. This is not erring on the side of caution. The preamble to regulations helps to clarify the regulations. In cases where there may be residual ambiguity in regulations, and no relevant guidance exists, the

198 http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm115989.htm.

manufacturer should have a reasonable basis for their actions related to the regulation and document that basis.

5. On page 10 Dr. Pence states, "FDA may require conduct of clinical trials to substantiate the safety and effectiveness of a device in approximately 10-15% of cases and may also require postmarket surveillance to obtain 510(k) clearance." First, although Dr. Pence implies that the 510(k) process is less stringent than the PMA process due to the low percentage of 510(k)s with clinical data, it is notable that the TVT Classic 510(k) contained clinical data. Second, postmarket surveillance is a required element of the quality system regulation and a requirement under the MDR regulation. Postmarket surveillance is not optional for any Class II device.

6. On page 11 Dr. Pence refers to devices found NSE by FDA as "novel." FDA does not describe a device found not substantially equivalent (NSE) as novel, just not equivalent to the claimed predicate. The options for the 510(k) submitter faced with an NSE determination depend on the reason for NSE. If the NSE reason is the device presents new questions of safety and effectiveness then, if the decision is sustained after any appeal, no manner of additional data will overcome that finding.

7. On page 12 Dr. Pence states, "...PMA is generally required for Class III devices that are determined to be either novel or pose a significant risk of illness or injury." The TVT Classic device is Class II therefore by her statement it is not "novel" nor does it pose a significant risk of illness or injury. If FDA believed otherwise they could propose reclassifying this type of device, which they have not.

8. On page 12 Dr. Pence refers to "valid scientific evidence" solely related to PMA applications. According to 21 CFR §860.7 valid scientific evidence applies to the determination of safety and effectiveness for both Class II and Class III devices.

9. On page 12 Dr. Pence states that a Class III device introduced into commerce without an approved PMA is adulterated and misbranded. This is not the case. According to 501(f) (21 USC §351(f)) of the Act this prohibited act is only an adulteration. In a similar way, the lack of a 510(k) is only a misbranding. When FDA becomes aware of a device on the market without clearance or approval the agency brings charges of both adulteration and misbranding since it cannot assume the ultimate classification of the device.

10. On page 14 Dr. Pence describes fair balance regulations applicable to drugs. These regulations do not apply to devices. FDA cannot base device enforcement actions on drug rules. Any and all references to drug rules are completely irrelevant to this litigation.

11. On page 15 Dr. Pence refers to a K86-3 Blue Book memo which states that a 510(k) must contain labeling only sufficient to describe the device's intended use while PMA labeling is approved as part of the PMA. The implication is that FDA does not evaluate labeling in a 510(k). In the case of the TVT Classic, K974098, on 14 January 1998,

FDA requested Ethicon to amend the labeling during its review of the 510(k).[199] FDA's recommendations included the following:

Indications for Use (add in bold)
The Tension Free Vaginal Tape (TVT) device is a sterile, single-use device intended to be used as a pubourethral sling indicated for treatment of stress urinary incontinence (SUI), **for female urinary incontinence resulting from urethral hypermobility or intrinsic sphincter deficiency.** The TVT Introducer and Rigid Catheter Guide accessories are intended to facilitate placement of the TVT device. The accessories, available separately, are provided non-sterile and are reusable.

Please add the following statements to your labeling:
Warnings
- following a Bladder Neck Suspension procedure, the patient should be counseled that future pregnancies may negate the effects of surgical procedure and the patient may again become incontinent.
- transvaginal sling procedure the patient should be counseled to avoid physical strain and lifting for 2-3 months post procedure.

Adverse Effects
- over correction may cause temporary or permanent lower urinary obstruction.

Please modify the instructions for use to better describe the method of placement. This change should include:
- how the tape is passed under the mid urethra;
- instruments used; and
- the extent of dissection needed.

Ethicon responded on 21 January 1998 with amended labeling.[200] It is clear from the FDA memo that FDA thoroughly evaluated the draft TVT Classic labeling including the contraindications, warnings, precautions, adverse reactions, and actions. The FDA comments exhibit FDA's understanding of the device, the surgery, the submitted documents including the clinical data, and the associated complications. The FDA comments on warnings and adverse effects also indicate its awareness of information not included in the TVT Classic submission.

12. On page 15 Dr. Pence refers to human factors evaluations by the Division of Device User Programs and Systems Analysis (DDUPSA). This program expired long before I retired from FDA in 2011. There has been no DDUPSA in FDA's organization for quite some time.[201]

13. On page 17 Dr. Pence discusses advertising. There are several issues with her description:

First, the appellate court decision to which she refers is based on a drug case in which advertising accompanied the product. The ruling falls short on advertising that does not accompany a product, and this can occur.

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[199] ETH.MESH.08476217.
[200] ETH.MESH.08476218-08476224.
[201] CDRH org chart, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHOffices/ucm127854.htm

Second, she refers to Docket 2005N-0354[202] which was an FDA activity related to Direct to Consumer (DTC) Advertising. Since TVT devices are not restricted devices they are not subject to the act's regulations on DTC advertising. In fact, FDA has not pursued device guidance on this topic.

Third, she again refers to drug regulations and not device regulations as a basis for her statements. Drug regulations do not apply to devices and cannot be used as a basis for device enforcement actions.

Fourth, she states that FDA cannot require prior approval of the content of advertisements except for those considered labeling. For a 510(k) device a significant change to labeling will require a new 510(k).[203]

14. Dr. Pence lists provisions of misbranding on page 18, however item (2) does not apply to the TVT Classic since it is not a restricted device, item (3) does not apply to the TVT Classic since FDA or even Dr. Pence in her report has not declared the TVT Classic to be misbranded under this specific provision, and item (4) is misstated by her in that this specific misbranding provision refers to "adequate directions for use." Prescription devices like the TVT Classic are exempt from adequate directions for use under 21 CFR §801.109 provided they are under the supervision of a licensed practitioner and labeled according to this regulation.

She also refers to materiality in FDCA §201(n). Materiality relates to an important fact and knowing the fact would change a decision. I will discuss this aspect in a later comment on MDRs.

15. On page 18 Dr. Pence refers to guidance when describing misbranding and fair balance. There is no device statute or device regulation specifically regarding "fair balance" in labeling or advertising. Statements in guidance are not enforceable unless they are stating a statutory or regulatory provision.

16. On page 19 Dr. Pence refers to false or misleading labeling guidance, which is not enforceable.

17. On page 20 Dr. Pence refers to “Dear Health Care Professional" letters and to related drug guidance. This guidance does not apply to medical devices. The specific device guidance she references applies only to the relevant products mentioned in the guidance.

18. Contrary to her report on page 24, there is no firm definition of "reasonably suggests", per se, in the definitions section of the MDR regulation, 21 CFR §803.3. Rather, the MDR regulation, 21 CFR §803.20(c), only identifies the type of information that "may reasonably suggest" that a reportable event has occurred. It is a somewhat open to interpretation explanation. In comparison, the explanation of the term "reasonably known" in 21 CFR §803.50(b) is more definitive.

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[202] Transcript regarding Docket 2005N-0354, http://www.regulations.gov/#!documentDetail;D=FDA-2005-N-0162-0040.
[203] 21 CFR §807.87(a)(3).

19. On page 25 Dr. Pence refers to serious injuries, which must be reported to FDA. This is not entirely the case. Only serious injuries meeting the definition in 21 CFR §803.3 must be reported.

20. On pages 26-27 of her report Dr. Pence includes the following provision of the MDR regulation:

> A manufacturer does not have to report an adverse event if it has information that would lead a person who is qualified to make a medical judgment to reasonably conclude that a device did not cause or contribute to a death or serious injury.[81] Persons qualified to make a medical judgment include physicians, nurses, risk managers, and biomedical engineers. The manufacturer must keep in its MDR event files the information that the qualified person used to determine whether or not a device-related event was reportable.

Based on this regulatory requirement Dr. Pence is not qualified to make medical judgments on whether a device did or did not cause or contribute to a death or serious injury. She is not a physician, nurse, risk manager, or biomedical engineer. On the other hand, FDA classified me as a Supervisory Biomedical Engineer based on experience, training and knowledge.

21. It is important to note that submission of an MDR is not an admission of a causal or contributory relationship of the event to the device. Dr. Pence notes this in her report on page 27. The manufacturer may determine causality or contribution as a result of its investigation of the event. FDA conducts MAUDE searches but is careful to indicate that the results are associated with use of the device without assigning causality. In other words, statistics on patient outcomes based on MDR reports always has the caveat that some percentage of those outcomes may not be device related.

22. On pages 29-30 Dr. Pence refers to underreporting of adverse events. I note that her references are at least 7-9 years old. FDA has made a conscious effort to improve reporting, for example with the MedSun network of hospitals. Manufacturers rely, in part, on health care facilities to be compliant with the MDR regulation. Manufacturers can report only what they become aware of from health care facilities and from their own sources. I am not aware of evidence indicating Ethicon did not control and process reports it received. Also, Ethicon did not rely solely on MDR reports to gauge the performance and safety of their devices; they also proactively reviewed literature and other sources of information.[204]

23. On page 401 Dr. Pence states that Ethicon did not disclose financial conflicts of investigators to FDA in the K974098 submission. The rule regarding financial disclosure by investigators became effective February 2, 1998. The TVT Classic 510(k) was submitted on October 29, 1997 and found equivalent by FDA on January 28, 1998.[205] Accordingly, Ethicon was not required to submit a disclosure to FDA.

24. Contrary to her opinion 1, it is documented in K9704098, and in Design History Files that Ethicon verified and validated the safe and effective use of the TVT Classic and FDA found the device substantially equivalent. The FDA, in its retrospective analysis of the TVT devices with the assistance of a panel of experts, declared at the conclusion

[204] See the Ethicon Clinical Reports, e.g., ETH.MESH.00831362.
[205] ETH.MESH.09476211.

of the panel review that "The panel consensus was that the safety and effectiveness of these devices is well-established."[206]

25. Dr. Pence's report includes several pages on physician and patient labeling. I have the following comments on her opinions or statements:

Although I am not a physician, nor is Dr. Pence, it is my experience in working side by side with physicians over the years on labeling issues that they have a different perspective on labeling than non-physicians. Ethicon medical director testimony reflects this perspective of doctors as follows, for example:

On page 56 Dr. Pence does not completely quote Dr. Hinoul when asked about complications listed in the FDA statement in labeling. His testimony (emphasis added) for her footnotes 219-220 references was "Yes. Not necessarily with the same words, but they will be reflected in the labeling, yes."[207] He also believed that complication lists should be "complications specifically related to our device." and not "...every complication possibly associated with an type of surgery should be included..."[208] This illustrates the doctor's perspective, i.e., interpretation of terms, the fundamental knowledge of doctors, and the focus in labeling on what is unique to the device.

I give one more example. Dr. Pence refers to Dr. Weisberg's testimony on page 58 on dyspareunia. Dr. Weisberg testified "Those words are not in there, but it is certainly dealt with when they talk about erosion and they talk about injuries to nerves. And every doctor knows that scarring can cause pain. It's a given. It's a basic."[209]

I believe the perspective of the Ethicon medical directors invokes the permissible regulatory exclusion of "directions, hazards, and warnings, and other information that is commonly known to practitioners" for prescription devices under 21 CFR §801.109(c).

In Part 3 beginning on page 58 Dr. Pence describes the literature concerning TVT surgeries. This brings up a studied point on IFUs. Studies have concluded that doctors do not rely primarily on the IFU for information regarding devices but rather on the literature and other sources of information.[210] Indeed, board certification requires continuing education to maintain physician knowledge in their area of expertise.

Part VIII.B. of her report starting on page 74 refers to patient labeling. Generally, there are no regulatory requirements for patient labeling for a 510(k) prescription device and for the contents of such labeling. Any labeling must not be false or misleading. The FDA guidance related to patient labeling referenced on page 79 is not enforceable.

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[206] FDA 24 hour memo, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM271769.pdf.
[207] Hinoul, 6/27/13, page 557:5-7.
[208] ID. page 571:12-17.
[209] Weisberg, 8/9/13, page 722:17-21.
[210] example, Haug, J.D., Physicians preferences for information sources: a meta-analytical study, Bull Medical Library Assn, 1997 July;85(3):223-232.

On page 84 Dr. Pence proffers the view that the patient brochures and the prescription labeling were misbranded. I disagree based on: Dr. Pence's one-sided analysis of facts and testimony for which I have provided a couple examples where the factual testimony paints a different picture; the lack of any FDA enforcement regarding Ethicon TVT labeling that has been in full view of FDA before and since FDA began generating its SUI web site information; lack of sufficient regulatory foundation, i.e., lack of patient labeling requirements and allowable medical judgment on the content of prescription labeling.

26. I believe her Section VIII stating labeling was inadequate and did not support adequate patient counseling, misses a major point. The point is the process of patient counseling and informed consent. FDA regulates informed consent only when it is part of an investigational study. Still, FDA has weighed in on the informed consent process for SUI treatment in its public health statements that I describe in my report. In the FDA SUI Information for Patients the key phrase is "ask your surgeon." It doesn't say to the patient, "read the brochure."[211] The advice to surgeons is obtain specialized training, be vigilant, and inform the patient of options and risks, all of which that are listed may be considered basic by a physician. It does say provide a brochure, if available but this is supplementary to the process.

27. Beginning on page 99 Dr. Pence asserts that 29 events documented in issue reports out of 258 events that were not reported as MDRs by Ethicon should have been submitted by Ethicon as MDRs. She does not describe the methodology for selecting the 29 events and whether these were the best examples to support her opinion. In every comment on an event she contradicts Ethicon medical opinion on matters such as causation, intervention, diagnosis, and prognosis but as I noted earlier in comment 20 she is unqualified to make these judgments according to regulation.

Dr. Pence notes that Ethicon submitted 603 MDRs or 70% of the events reported to it. To me this is clear evidence of Ethicon's compliance with the MDR regulations.

I also examined the issue reports as noted in my report. The issue reports to which she refers provide evidence of follow up on events by Ethicon.

Even if I were to presume Dr. Pence is correct in all her assessments of the 29 issue reports and Ethicon submitted all of them to FDA as MDRs would it materially change the MDR statistics and FDA's decisions? My opinion is no. The numbers are too small to make enough of a difference in the statistics.

In her report on page 108 Dr. Pence refers to an FDA inspection in 2005 and a Form 483 observation on complaint handling related to 5 events. A Form 483 observation is not a violation. Ethicon responded quickly and thoroughly.[212] FDA issued no Warning letter based on this observation.

Dr. Pence concludes that the TVT devices are misbranded due to deficient postmarket vigilance but FDA has never cited Ethicon for a

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[211] http://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/urogynsurgicalmesh/ucm345230.htm.

[212] First response, ETH.MESH.00330769-00330775.

violation of postmarket activities related to the TVT devices. It is my opinion that Ethicon was substantially compliant with their postmarket obligations as I note in my report.

I reserve the right to amend my opinions pending further discovery.

Executed in Herndon, Virginia on February 24, 2016.

Timothy A. Ulatowski

TVT gen

APPENDIX A: CV

CV

Timothy A. Ulatowski

[redacted]

[redacted] [redacted]

Regulatory Consultant/Medical Devices

Extensive Regulatory Experience ~ Risk Management ~ Technical Expert

A unique medical device consultant with extensive experience in both premarket evaluation of new medical devices and enforcement of FDA laws and regulations. Over 40 years of significant public health achievements, creating major regulatory programs and policies, developing and implementing strategic and risk management plans, and building collaborations with global regulatory partners and industry. Proven skills in advising industry on regulatory issues, assessing compliance and enforcement actions, evaluating premarket documents, managing and supervising large organizations, resolving complex technical and scientific problems of individual firms to those of national and international scope, and communicating to diverse audiences.

Selection of Notable Accomplishments

Technical leadership on numerous compliance, enforcement and recall actions, many of national or global importance

Initiated use of novel corporate enforcement actions

Created effective internal quality management system used as a model program in FDA

Lead author of international guidance documents on aspects of the Global Harmonization Task Force medical device regulatory model adopted by many countries

Recognized in “Top 100” of medical device professionals/MDDI

Primary FDA reviewer of hundreds of Premarket Notifications, Investigational Device Exemptions, Premarket Approval Applications, recalls and compliance actions

Leader of team that developed the current FDA device standards program

Author of many key FDA premarket guidance documents, technical standards and publications

Senior advisor to DOJ and FDA criminal investigations office

Lead for agency on many GAO, OMB and Congressional activities

FDA spokesperson to major press and to large audiences

HHS Team Leader and technical expert remediating Anthrax contamination of Senate and Postal Service buildings

Creator of FDA/CDC/EPA tripartite collaborations on chemical germicides and co-author of current FDA/EPA national regulatory scheme for chemical germicides

Co-author and collaborator on sharps injury prevention guidance, related OSHA and NIOSH regulations and policies, resulting in documented reduction of injuries

Recipient of numerous major FDA awards

Expert witness for Defendants and Plaintiffs in numerous litigations; deposition and court testimony

Expert trainer on behalf of FDA and US Dept of Commerce for foreign regulatory staff and FDA staff

Successful, numerous premarket, postmarket and compliance accomplishments for large and small manufacturer or entrepreneur clients

Professional Experience

Regulatory Consultant, Medical Devices

April 2014 - Present

- Regulatory consulting support to the medical device industry in areas of premarket, postmarket, compliance, and combination products
- Expert witness in litigation

NSF Health Sciences (formerly Becker & Associates Consulting Inc.): Vice President, Regulatory and Compliance

June 2012 – April 2014

- Ensured effective and timely solutions to a variety of FDA regulatory and legal issues
- Provided expert advice and recommendations on premarket, quality systems, compliance and device reporting
- Trained industry staff, international regulators and FDA staff on FDA medical device regulations and procedures
- Served as expert witness in litigation

NDA Partners LLC: Principal

January 2011 – June 2012

- Advised clients on FDA regulations and law regarding product submissions, compliance and enforcement actions, and postmarket surveillance activities
- Served as an expert witness in litigation
- Conducted due diligence

FDA, CDRH: Director, Office of Compliance and Senior Advisor for Enforcement

January 2003 – January 2011

- Managed and supervised office of four divisions and 180 professional staff responsible for ensuring compliance with medical device laws and regulations
- Directed FDA device quality system and bioresearch enforcement programs
- Directed inspection assignments and assessed quality system and bioresearch monitoring inspection reports and company/investigator/sponsor/IRB responses to determine violations
- Worked with all FDA districts, ORA and drug, biologics and food compliance executives to formulate enforcement strategies and actions

- Hands on evaluation and management of recalls, device advertising and promotion, MDRs, registration and listing, and medical device field resource allocation and prioritization
- Created new device enforcement policies and programs, directed implementation of the Commissioner's strategic action items, and participated in executive strategic planning at the agency and center levels
- Co-leader of FDA Medical Device Field Committee, an ORA/CDRH collaboration
- Initiated comprehensive training program for compliance staff and web-based information for the public
- Co-leader of 2010 user fee legislation post market committee, devising proposals and strategies with key Center and Agency staff for next round of legislation
- Senior Device Enforcement Advisor September 2010 – January 2011

FDA, CDRH: Head of USA Delegation, Global Harmonization Task Force and FDA representative to GHTF Study Group 1 Premarket

January 1995 - October 2010

- Managed the activities of the USA FDA participants to the GHTF Steering Committee and the five study groups; collaborated with USA industry task force members, USA leader on the GHTF Steering Committee for last four years
- Coordinated creation and review of documents and recommended agency decisions on pending documents to Center Director
- Primary author of several GHTF documents, including the original premarket "STED" document, and Global Model document, which are now used internationally
- Frequently trained international government staff on GHTF and FDA procedures

FDA, CDRH/Office of Device Evaluation: Director, Division of Dental, Anesthesiology, General Hospital, and Infection Control Devices

December 1996 – January 2003

- Managed premarket activities, such as review of premarket submissions and investigational applications, panel meetings, guidance development, and collaborative support for other CDRH offices
- Led development of the division during a major reorganization
- FDA lead on numerous international standards committees, reengineering task groups, and interagency task forces dealing with significant public health issues
- Succeeded in reducing review times while improving the quality and rigor of reviews
- Primary reviewer on numerous 510(k)s, IDEs, and PMAs
- Agency and ISO technical expert on medical device sterilization and disinfection

Prior FDA experience, short summary

Device Evaluation Associate Director, Branch Chief and front line 510(k), IDE, and PMA reviewer

Director, Investigational Device Staff, IDE application review and protocol advice

New Drug Evaluation Product Manager, NDA and IND review and advisory committee exec sec

Microbiologist, National Center for Antibiotic Analysis, drug assessments

Prior to college and FDA career: US Army 1968 – 1971

Education

- Master of Science/Physiology with Biomedical Engineering emphasis, 1988 GPA 4.0

Georgetown University School of Medicine

- Bachelor of Science/Microbiology, 1974 cum laude

Pennsylvania State University

- Food and Drug Law, George Washington University School of Law, 1978

- Computer Science, University of Maryland and Charles County Community College, 2000-2005

- Numerous FDA sponsored or supported courses, for example, in risk management, quality systems, clinical studies, human factors, statistics, sterilization engineering

APPENDIX B: Materials Reviewed and Public Sources of References

Public Sources of References to Food and Drug Laws, FDA Regulations, FDA Guidance, FDA Policy and Procedures, and Definitions

Federal Food, Drug, and Cosmetic Act:
http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/default.htm

21 Code of Federal Regulations:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

FDA Guidance and Policies: www.fda.gov

Merriam-Webster Online Dictionary

Global Harmonization Task Force web site, www.ghtf.org

Additional references list to be supplied by Butler Snow.

APPENDIX C: Prior Testimony

University of Pittsburgh of the Commonwealth System of Higher Education d/b/a University of Pittsburgh v. Varian Medical Systems, Inc.

Civil Action No.: 2:08-cv-01307 (USDC, Western District of Pennsylvania)

David M. Kloss, et al, v. I-Flow Corporation, et al, Case No. 2:10-cv-00295-JFC (USDC, Western District of Pennsylvania)

Retractable Technologies, Inc. and Thomas Shaw v. Becton, Dickinson and Company, Civil Action No.2:08-cv-16 (Folsom) (USDC, Eastern District of Texas Marshall Division)

Diagnostic Devices Inc, v. Pharma Supply, Inc. et al, Diagnostic Devices Inc, v. Taidoc Technology Corporation, Case No.3:08-CV-00149-MOC-DCK (USDC, Western District of North Carolina, Charlotte Division)

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-CTL] (Superior Court of the State of California In and For the County of San Diego, Central Branch)

Superior Court of New Jersey, Law Division, Atlantic County

In re Pelvic Mesh/ Gynecare Litigation, Case No.291 CT, Master Case 6341-10

Jackson, et al v DePuy Orthopedics, No. CAL 10-32147 (Prince George's County, MD)

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit Court, Cook County, Illinois)

Dorney-Madgitz v. DePuy Orthopedics, Inc., et al., 5:11-cv-001240-RBS (USDC, Eastern District of Pennsylvania)

Weinstat, et al. v. Dentsply International, et al., San Francisco Superior Court No. CGC-04-432370

Braun v. Medtronic Sofamor Danek, USDC, District of Utah, Central Division, Case 2:10-cv-01283

Connie Schubert and Kevin Schubert v. Ethicon, Inc., Ethicon Women's Health and Urology, a division of Ethicon, Inc., Gynecare, and Johnson and Johnson, et. al., In the Circuit Court of Jasper County, Missouri at Joplin, Case No. 10AO-CC00219

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York, Case 1:12-cv-03479-SAS (for Plaintiff)

Carol Lewis and Kenneth Lewis v. Ethicon, USDC, Southern District of West Virginia, MDL No. 2327

April Christine Cabana v. Medtronic Inc. (et al), Superior Court of the State of California, County of Los Angeles, Case No. BC 465 313

Christine Napolitano v. Synthes, Inc., USDC, District of Connecticut, Civil Action 3:09-CV-00828

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC, Northern District of Texas, Dallas Division)

City of Lakeland Employees Pension Plan v. Baxter International Inc., No. 10-cv-6016, USDC, Northern District of Illinois

Smith v. Baxano, Inc. et al, Superior Court of Washington for Snohomish County, Case No. 13-2-02714-1

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa County, Oklahoma, No. CJ-2011-05804

Zimmer NexGen Knee Implant Products Liability Litigation, USDC, Northern District of Illinois, Eastern Division, MDL No. 2272, Master Docket No.:1:11-cv-05468

Sandra Garcia v Rodolfo J. Walss, MD, Johnson & Johnson, Inc. and Ethicon, Inc., District Court, 103rd Judicial District, Cameron County, Texas, Cause No. 2013-DCL-3511-D

Laura Ness v Depuy Orthopedics, Inc., et al., In the Circuit Court for Baltimore City, Case No. : 24-C-14-002465

Consolidated Fresenius Cases, Commonwealth of Massachusetts, Middlesex SS., Superior Court Department of the Trial Court, Civil Action No. 2013-03400-O Session

Aoki, Christopher, Greer, Klusmann, Peterson, Thibodeau (separate Plaintiffs) v DePuy Orthopedics, Inc. et al,. USDC, Northern District of Texas, Dallas Division, MDL No. 2244

Center City Periodontists, P.C., et al. v. Dentsply International, Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.

Michael Parker, Individually and Amy Parker, Individually v. Veronica A. Vasicke, MD; Bluegrass Orthopedics & Hand Care, PSC; and I-Flow Corporation, Fayette Circuit Court, Eighth Division, Civil Action No. 12-CI-3543.

Court Testimony:

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit Court, Cook County, Illinois)

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-CTL] (Superior Court of the State of California In and For the County of San Diego, Central Branch)

Weinstat, et al. v. Dentsply International, et al., San Francisco Superior Court No. CGC-04-432370

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York, Case 1:12-cv-03479-SAS

Becky S. Anderson v. Medtronic, Inc. (et al), Superior Court for the State of Washington, County of King, No. 12-2-17928-0 SEA

Donald Gustafson v. Zimmer, Inc., District Court, Collin County, Texas, 366th Judicial District, Cause No. 366-03111-2011

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC, Northern District of Texas, Dallas Division)

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa County, Oklahoma, No. CJ-2011-05804

Alysia Ogburn-Sisneros, as personal representative of the estate of Billy Ogburn, Sr., Plaintiff v. Fresenius Medical Care Holdings, Inc.d/b/a Fresenius Medical Care North America, Inc, Fresenius USA, Inc., Fresenius USA Manufacturing, Inc., Fresnius USA Marketing, Inc., and Fresenius USA Sales, Inc., Defendants, Commonwealth of Massachusetts, Superior Court Department, Civil Action No. 13-5050

Center City Periodontists, P.C., et al. v. Dentsply International, Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.